



# MEDICINE

*Analytical Reviews*

of

General Medicine  
Neurology and Pediatrics

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THE WILLIAMS & WILKINS COMPANY  
BALTIMORE, MD  
1927









# THE RELATION OF THE HYPOPHYSIS TO DIABETES MELLITUS<sup>1</sup>

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It is generally considered that the hypophysis is concerned in the metabolism of carbohydrates and that it is a factor in the production

## CORRECTION

*Medicine*, Vol V, No 4, page 384, Table 1, add after Hippocrates

	1	2	3	3a
Hallé- Husson (1821)	Tempéramens parties	Abdominale	Thoracique	Céphalique
Rostan (1828)	Type musculaire	Digestif	Respiratoire	Cérébral

published the first reports of the distinct clinical entity which he named acromegaly (2), noted that diabetes existed in two of his first four cases (2, 3, 5) as well as in an appreciable number of the cases identified as acromegaly which had been reported by other authors under various names (4), and wondered whether the acromegaly or the diabetes was responsible for the thirst and polyuria noted in these cases (4, 5). Following Marie's identification of acromegaly, case reports accumulated in the literature which were collected and studied, with the result that Marie's observations were confirmed, and, recognizing that diabetes in acromegaly was of more than coincidental frequency, the students of diabetes attempted to explain their relation

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Loeb (6), calling attention to the sugar punctures of Bernard, Schiff and Eckhard, suggested that the glycosuria was neurogenic in origin, i e, that the hypophyseal tumor found so frequently in these cases caused glycosuria by pressure on a neighboring "zuckerzentrum". Naunyn (7) gave credence to this view. Lorand (8) objected to the theory for the reasons that there were cases of hypophysis and brain tumor with compression phenomena in which glycosuria was absent, and likewise cases of acromegaly with diabetes in which there were no signs of compression. He pointed out that there were many reasons to believe that changes exist in the thyroid as well as the hypophysis in acromegaly, and suggested that a disturbance of the internal secretion of the thyroid was responsible for changes in the functional ability of the islands of Langerhans resulting in diabetes. Hanseemann (9), Dallemagne (10) and Pineles (11) each observed cases of acromegaly with diabetes in which the pancreas was found at autopsy to be diseased, and believed that this was the cause of the diabetes of acromegaly. Borchardt (12) found that glycosuria was rare in cases of hypophyseal tumor with no acromegaly, and proposed that since acromegaly was probably due to an excess of hypophysis secretion, and since he was able to produce glycosuria in animals by administration of hypophysis extract, the glycosuria of acromegaly was due directly to an excess of pituitary secretion. Other authors, von Noorden (13), Lepine (14) and Magnus-Levy (15), admitted the significant frequency of diabetes in acromegaly and noted these various theories, but stated that an adequate explanation was impossible until more facts were available, and reserved their opinions. Cushing and his associates (16) were the first to attack this problem directly and in detail, and while their findings will be discussed more fully later, it is sufficient here to state that among other things they concluded that an excess of secretion from the posterior lobe of the hypophysis causes glycosuria, while a deficiency of this secretion results in an increased tolerance for carbohydrates.

In order to form an opinion as to the validity of any of these theories or to decide whether any of them sufficiently explains the facts it is necessary to collect and analyze the observations which contribute to our present knowledge of the relation of the hypophysis to carbohydrate metabolism. The text which follows is intended to provide

the data for such a study. For convenience it is divided into two sections, (a) including the facts obtained by clinical investigations on human subjects with various hypophyseal disorders, and (b) the data obtained by animal experimentation.

#### CLINICAL STUDIES CONCERNING THE RÔLE OF THE HYPOPHYSIS IN CARBOHYDRATE METABOLISM

##### *Diabetes in acromegaly*

The frequent occurrence of diabetes or glycosuria in acromegalic patients is indisputable. By accumulation of case reports Hanseman (9), Hinsdale (17), Williamson (18), Borchardt (12), Anders and Jameson (19), and Rosenberger (20) found the frequency with which diabetes or glycosuria occurred in acromegalics to be respectively 12 in 97, 14 in 130, 6 in 21, 71 in 176, 16 in 88 and 82 in 196 cases, the figures in the largest series, those of Borchardt and Rosenberger, indicating an incidence of over 40 per cent. Furthermore it is probable that this reported frequency is lower than that which actually exists, partly because many of the older case reports contained no record of the presence or absence of glycosuria, and also because it is probable that some of the cases reported as negative had evidence of diabetes not manifest at the times when they were studied. At any rate it may be said with certainty that the outstanding reason for considering the hypophysis as in some way related to diabetes is that glycosuria is more than coincidentally frequent in acromegaly.

The symptoms of acromegaly practically always antedate the appearance of sugar in the urine, although in a case of Schlesinger's (21) the diabetes appeared before any sign of acromegaly was evident. Labbe reported a case (22) in which the glycosuria appeared twenty-three years after the onset of the acromegaly. This case was one of gigantism, as are most of the others in which this interval has been long. In the large majority of cases of true acromegaly but a few years at most have intervened between the onset of symptoms of the two disorders.

Marie first made reference to the excessive thirst and urinary output which usually accompany the diabetes and in this respect the diabetes of acromegaly is similar to ordinary diabetes in most cases. These

symptoms are at their height at the beginning of the diabetes when it is uncontrolled and there is an excessive glycosuria, and they disappear as a rule when the glycosuria is reduced by suitable dietetic management, except of course, in diabetes insipidus which is not uncommon in acromegaly. Frequently the glycosuria is intermittent or present only after ingestion of large amounts of carbohydrate. Thus, as in ordinary diabetes, the glycosuria may be detected only after excessive sugar ingestion. It may appear spontaneously without symptoms, or it may be accompanied by thirst, excessive urination and other symptoms which are so characteristic of true diabetes mellitus when large quantities of sugar are excreted. And, as in ordinary diabetes, these differences are doubtless largely due to the differing degrees of glycosuria.

It has been difficult to draw a satisfactory conclusion as to the important question of the course of the diabetes of acromegaly. There is no comprehensive survey of individual case reports in the literature which would throw light on this particular point, and in this study no attempt has been made to cover all of the case reports. Even if this were done, there are reasons to doubt that sufficient information exists to permit of a definite conclusion, because reports of continuous consecutive observations of single cases up to the time of death are exceptional. Most of the case reports consist either of clinical observations up to a certain point in the course of the disease with no subsequent data to the time of death, or of records of the findings at autopsy with a dearth of clinical data. Furthermore, it is only within comparatively recent times that quantitative studies of the diabetic metabolism have been consistently reported in any type of diabetes and it is therefore difficult to determine from the information available in many of the older reports, the actual degree of diabetes at different periods of its course in acromegalic patients. While such quantitative data would probably not be essential in most cases, it is obvious that the combination of an insufficiency and inexactness of data in the literature concerning the course of the diabetes from beginning to end makes a description of the natural course of the diabetes of acromegaly impossible. Nevertheless, we may assemble the available information relative to this point.

Lepine (14) held that the diabetes of acromegaly is relatively mild

although many cases excrete much sugar on occasion. He knew of only one case which died in coma (that of Stadelmann). Naunyn (7) cited the cases of Stadelmann, Cunningham, Marinesco and Hansemann as examples of severe diabetes in acromegaly with heavy sugar excretions. Labbé (22) noted that the diabetes tended to be mild in the cases he saw but that in some it was severe, with denutrition and death in coma. Koopman (23) enumerated the cases of Bury, Stadelmann, Strumpell, Hinsdale, Ravaut, Dallemagne and Umber which died in coma. Magnus-Levy (15) stands alone in the view that "The diabetes has no clinical distinctions nor metabolic features different from those of ordinary diabetes" (p. 1018).

Various statements recur in the literature of acromegaly with diabetes to the effect that the diabetes is often observed to run an irregular or atypical course. Different types of behavior have been described, but as they are all similar in some respects they will be discussed collectively.

Sternberg (24) first called attention to the fact that the glycosuria might vary independently of the diet, and later von Noorden, who is usually cited as the first to have made this observation, stated (25, p. 47) "*Die Glykosurie der Akromegalen zeichnet sich oft durch grosse Schwankungen aus und folgt nicht so regelmässig, wie die Glykosurie des gewöhnlichen Diabetes, dem Wechsel des Nahrungszufuhr*". Borchardt studied all of the cases of acromegaly in the literature up to 1908 (12) and found that the tolerance occasionally fluctuated greatly, and at times the diabetes apparently disappeared spontaneously. Cushing and his associates (16) noted that diabetes, glycosuria or lowered tolerance for carbohydrates usually occurred in the early stages of acromegaly, while later, an increased tolerance, often considerably above the normal, supervened. Other references to the atypical behavior of the diabetes of acromegaly, variously called fluctuation of glycosuria or tolerance, disappearance of diabetes, acquisition of abnormally high tolerance late in the acromegaly, are found in the writings of Froment (26), Macleod (27), Kraus and Reisinger (28), Labbé (22), Ellis (29), Koopman (23), Goetsch (30), and Schlesinger (31).

Recognizing that phenomena of this type, which are exceptional in diabetes mellitus, might help to explain the pathogenesis of the dis-

as of acromegaly, the writer has attempted to collect and study these cases in which atypical or peculiar behavior was described in order to determine whether such behavior has actually occurred as commonly as is indicated by these statements in the literature. Fifteen cases were found all told in which the behavior of the diabetes was said to be noteworthy. The following descriptions of these cases include all the information given in each case that bears on the point in question.

During the year prior to the time of the following observation von Sorden (13) had seen five acromegalics, four of which were diabetic. In two of them the diabetes was in no way different from the ordinary type, while in the other two there were occasional fluctuations of the glycosuria which were independent of changes in the diet. Machwitz (14) presented a case of acromegaly with a high grade glycosuria in which the same behavior was said to have occurred (32). Strumpell (33) reported a case in which, during a five year period of observation ending in death, the diabetes appeared to run a variable course. Sometimes the urine contained much sugar and was made sugar-free by means of a diet consisting of meat and fat, while at other times it was entirely sugar-free on a diet rich in carbohydrate. There was no sugar in the urine at death. Edinger stated that in his case "wiederholt, ohne nachweisbaren Grund Zucker im Harn zu 7 und 9 Proz. aufgetreten und auch wieder verschwunden ist" (34, p. 197). As far as can be determined from the actual report, variations in the food supply are not excludable as the author does not describe the diet. Dr. Cushing has very kindly given the details of a phenomenon which occurred in one of his cases (unpublished). This patient, a man of forty-nine years, who was studied in 1916, had developed symptoms of acromegaly and diabetes simultaneously about four years before the time of study. He presented a characteristic picture of acromegaly with neighborhood and radiographic signs of a pituitary tumor with pressure, and an appreciable glycosuria which was reduced by diet. A few days after the patient was sent home he developed a severe headache, exophthalmos of the right eye, ptosis of the upper lid, diplopia, and an almost constant watery discharge from both nostrils (rhinorrhea?). Within a week after this attack the headaches disappeared, and in spite of an un-

restricted diet the urine was sugar-free. Nearly two years later the patient reported that no headaches or glycosuria had recurred. The blood sugar was then normal and he had gained thirty pounds in weight. Another letter about six years later stated that the nasal discharge was still present and that there had been "no glycosuria for a week," so the disappearance of glycosuria apparently was not permanent.

In other cases the glycosuria has disappeared and not been observed to recur. This cannot be taken to mean a permanent disappearance of the diabetes because it is obvious that a permanent disappearance could only be demonstrated by continuous observations until the time of death, which has been exceptional in these case reports.

Finzi (35) was the first to report permanent disappearance of diabetes in acromegaly. In his case the acromegaly was accompanied by a diabetes of nine years duration which later vanished according to his statement. In Buday and Jancso's acromegalic giant (36) the diabetes disappeared eight months before death, when the patient became very ill from a rapidly advancing pulmonary tuberculosis. Schlesinger's acromegalic with diabetes (31) became sugar-free on diets yielding from 2000 to 2500 calories daily and glycosuria did not recur during the nine month period of observation although further additions up to 3500 calories were made. Whether or not the glycosuria ever returned is not stated. Borchardt (12) mentioned that a case which he observed in his own clinic had no glycosuria after ingestion of 150 grams glucose although diabetes had been observed five years before. He also refers to a case from the Lichtheim clinic which, he said, had diabetes earlier, "Jetzt keine alimentäre Glykosurie." One out of a series of acromegalics reported by Goetsch, Cushing and Jacobson (16), who was observed at the time of study to have a high assimilation limit (alimentary tolerance) for sugars had failed to pass a life insurance examination some years before as he was supposed to have been suffering from diabetes, and in still another case (37) there had been a suggestive polyuria with furunculosis five years before. Labbé saw a case with Langlois (22) in which symptoms of acromegaly developed at the age of twenty five and diabetes at forty eight. After the preliminary dietary control of the glycosuria there were indications that it never returned. Labbé (22, p 196) feels that



“ the glycosuria will spontaneously disappear towards the end of the disease, because, on account of the cachexia, the patient does not eat sufficiently.” In John’s case (38, 39) the symptoms of diabetes had dated back about three years and there was a heavy glycosuria when first observed. The urine was made sugar-free by diet and insulin. Three weeks later the diet was increased and the insulin stopped without glycosuria and after three months had passed, during which time the patient ate a liberal unmeasured diet which was unrestricted except for sugar and pastry, the urine was “sugar-free” and the fasting blood sugar level was normal. At this time the blood sugar curve following the ingestion of 100 grams glucose was found to resemble those obtained with normal individuals. The author concludes (p. 1631) “ a cure appears to have been established, as is indicated by the normal glucose tolerance curve . . . ” Otherwise this case and another studied by John possessed all the characteristics of true diabetes mellitus (39).

In his recent Cameron Lectures Cushing mentioned another example of the spontaneous disappearance of diabetes in acromegaly. The details in this case are not yet available as the lectures have not appeared in complete form at the present writing.

Ellis (29) described a case of acromegaly with diabetes which appeared to gain tolerance after removal of a pituitary adenoma. The diabetes in this case was of about 8 months duration and had led to acidosis. The urine desugarized in three days of fasting and remained “sugar-free” when the diet was built up to C 83, P 44, F 76. The operation was then performed. A trace of sugar appeared postoperatively, but thereafter for three years on a diet restricted only as to free sugar, the urine remained “sugar-free” and frequent fasting blood sugar estimations gave readings between 0.13 and 0.15 per cent. At this time glucose tolerance tests were made which were said to have shown some diminished carbohydrate tolerance. It may be pointed out that in this case the effect of the preliminary desugarization on the tolerance was not determined preoperatively, so it is not incontestable that the removal of the tumor alone was responsible for the increase of tolerance.

Goetsch, Cushing and Jacobson (16, p. 189) observed, “Our clinical studies make it apparent that in the early stages of acromegaly

the sugar tolerance is apt to be low but that later in the disease there is an acquired overtolerance" They determined the tolerance for sugar (as estimated by the amount necessary by mouth to produce mellituria) in a dozen cases of acromegaly in various stages of the disease and found that in most cases it was roughly proportional to the duration of the acromegaly. Indeed, this observation together with corresponding results obtained in studies with hypophysectomized dogs led Cushing to use the observed alimentary tolerance for sugar in a given case of pituitary disease as an indication of the existing state of glandular activity and the necessity for and dosage of hypophysis extract, on the hypothesis that (p 188) " in the early stages of the disease there is seemingly an activation of the posterior lobe leading, among other symptoms, to the glycosuria or lowered tolerance , in the later stages, a state of posterior lobe insufficiency supervenes, with an increase of carbohydrate tolerance "

### *Insulin in the diabetes of acromegaly*

Cushing (40) refers to the fact that the glycosuria and hyperglycemia of acromegaly react to insulin. Four instances of this have been reported, and the writer will add a fifth. Etienne, Drouet and Yovanovitch (41, 42) administered pancreatic extract (presumably insulin) to a case of acromegaly with glycosuria and observed that the glycosuria was reduced. Blum and Schwab (43) compared the action of 30 units of insulin on the blood sugar curves in cases of pancreatic and acromegalic diabetes. In both cases there was a substantial reduction of the previously existing hyperglycemia. Sachs and MacDonald (44) gave a brief description of a case of acromegaly which developed a transient glycosuria after removal of a pituitary adenoma, which was said to have been controlled by insulin. The case of John mentioned above shows a rapid disappearance of glycosuria and reduction of blood sugar level following the administration of insulin, but the effect of the insulin alone is not clear, because of the simultaneous institution of a measured diet which alone may have desugared. Finally, the case reported in the present paper shows how insulin reduced a constant glycosuria in a case of acromegaly with diabetes in a manner similar to that observed in ordinary diabetes mellitus.

*Pathological findings in the diabetes of acromegaly*

Pathological changes other than those found in cases of acromegaly without diabetes have not been recognized by those who have studied the pathology of acromegalic diabetic cases. The usual finding recorded has been tumor or hyperplasia of the hypophysis and nothing distinctive about the tumor has been observed in those cases with diabetes, although Dock stated that (45, p 812) "Diabetes is most marked with the largest tumors." In 1903 Launois and Roy (46) collected 16 cases of acromegaly with diabetes from the literature which included all that had been reported which had been necropsied. A hypophyseal tumor was present in every case.

Changes have been observed in the pancreas in a limited number of cases. Schutte analyzed the pathological findings in 49 cases of acromegaly in which the autopsy reports were satisfactorily complete (47). Pancreas abnormalities had been observed in 4 cases, 3 of which had been diabetic. Three of the 17 cases of acromegaly with diabetes collected by Pineles (11) showed changes in the pancreas. Rosenberger (20) and Kraus and Reisinger (28) each mention several other cases in their reviews of this subject. The writer has noted, in all, reports of 15 cases of acromegaly in which pancreas changes were described, namely, those cases of Dallemagne (fibrosis) (10), Hanse-mann (atrophy) (9), Brooks (atrophy) (48, 49), Fraenkel ("knotty hypertrophy") (50), Stadelmann (interstitial hemorrhagic pancreatitis) (51, 52), Pineles (suppurative pancreatitis) (53), Herxheimer, 2 cases (atrophy, hyalinized islets and atrophy, high grade sclerosis) (54, 55), Williamson (atrophy and fatty degeneration) (56), Steiger (sclerosis with diminution of islets) (57), Norris (58), Amsler (59), Cecil (60) (hyperplasia of islet cells), Kraus and Reisinger (scarcity of islets and atrophy) (28), and Kraus (61). Diabetes had been present in all of these cases except those of Stadelmann and Kraus and Reisinger.

An interesting and much-cited observation was made by Stadelmann, who reported 2 cases of acromegaly (52), one of which had had diabetes and died in typical diabetic coma. This patient was found at autopsy to have a normal appearing pancreas, while in the other case, with no diabetes, there were marked hemorrhagic changes in the pancreas.

There are but a few other pathological findings of interest. The thymus was not uncommonly found to be enlarged, the sympathetic trunks were hypertrophied in the cases of Lancereaux (62), Henrot (63) and Hanseemann (9), the cervical sympathetic ganglion cells were pigmented in Brooks' case (48), exophthalmic goitre was present in the cases described by Lancereaux (62), Henrot (63), Anders and Jameson (19) and Claude and Baudouin (64), and simple and adenomatous goitres were frequently observed. Pathological findings similar to these also have been described in cases of acromegaly without diabetes, indeed it may be stated with certainty that while changes are found in the hypophysis, pancreas, thyroid, adrenals, thymus, etc., in the diabetes of acromegaly, none of them are characteristic of those cases which have had diabetes, as similar observations have been made equally often in cases of acromegaly in which no diabetes has existed.

*The hypophysis in ordinary diabetes mellitus*

Recently a few authors have made reference to changes that occur in the hypophysis in ordinary diabetes mellitus. Fry studied the gland histologically in 8 cases of diabetes, 3 of acute pancreatitis and one of carcinoma of the pancreas, and stated (65 p. 288), "Definite histological changes occur in the anterior lobe of the pituitary in cases of diabetes in the form of adenomatous masses of eosinophilic cells, colloid invasion of the anterior lobe, and areas of cellular degeneration. Histological changes in the pituitary are absent or slight in cases of acute pancreatitis and carcinoma of the pancreas." Kraus later confirmed these observations in a study of the hypophysis in 23 cases of ordinary diabetes mellitus, 10 of which were between the ages of fourteen and forty-one and the others over forty-one. In all of the younger group and 2 of the older there were constant characteristic microscopical changes in the hypophysis in the nature of proliferation of the eosinophile cells of the anterior lobe (66). Furthermore, after total or nearly total pancreas extirpation in cats, he observed similar changes in the hypophysis (67).

*Case report of acromegaly with diabetes*

Before leaving the subject of the diabetes of acromegaly, the writer wishes to present the findings in a case studied on Dr Woodyatt's service at the Presbyterian Hospital, Chicago

M O, female, single, aged twenty-nine, was first seen in January, 1925 Her immediate complaint was that sugar had been discovered recently in the urine, and she desired treatment of her diabetes Her appearance was strikingly that of an acromegalic, however, and on questioning the following information was elicited



FIG 1



FIG 2

In the summer of 1922, two and one-half years previously at the age of twenty-six, frequent sharp headaches and irregular menstrual periods occurred simultaneously and the latter stopped three months later A year afterwards acquaintances called the patient's attention to the fact that her appearance was changing and she noticed then for the first time that her nose had increased in size, her cheekbones were more prominent, the skin of her face was becoming thick and furrowed, her fingers were thicker and stubbier, and she was wearing shoes and gloves  $1\frac{1}{2}$  to 2 sizes larger than she had before About this time she began to have attacks of agonizing pain in the left lumbar region and groin followed by blood in the urine, and

at one time she passed a stone through the urethra In September, 1924, approximately a year after the change in features was first noted, and two weeks after a tonsillectomy, she became very thirsty and passed large quantities of urine While on a low unmeasured diet she had become sugar-free and lost 21 pounds from her previous normal constant weight of 140 pounds since the glycosuria was discovered

*Examination* Body weight, 120 pounds (54 kgm) The patient was a well nourished, large-boned, muscular white woman with the typical appearance of acromegaly (Figs 1 and 2) The skin was faintly brown-tinged, of



FIG 3

coarse texture, oily, and contained many comedones The hair was profuse and of unusual distribution, heavy in the axillae and genital region where it tapered off toward the umbilicus in an inverted V-shape A dozen long black hairs encircled each nipple, and the forearms and legs resembled those of a hairy dark-complexioned man in hair growth The skin of the forehead was thick and deeply furrowed, the nose was coarse and much widened at the bridge and base with flaring nostrils The cheekbones and forehead were prominent, giving the eyes a sunken appearance and the chin was square The patient was of a masculine configuration with slender hips and heavy, well muscled arms and legs resembling those of a laborer,

and the fingers were thick, square-ended and stubby. The middle three fingers of each hand were approximately the same length, giving the hands a spade appearance (fig 3). The uterus was retroverted, about two-thirds normal size with a conical cervix the size of a small walnut. The visual fields showed no contraction perimetrically, the fundi appeared normal, there was no incoordination of ocular movements, and the olfactory sense was unimpaired. A complete neurological examination revealed nothing abnormal and physical examination of the lungs, heart, abdomen and blood vessels gave no further information of value.

TABLE 1

*Acromegaly diabetes Summary of metabolic data obtained in studies conducted at six-month intervals with diets of different glucose values*

DIET					MARCH, 1925— WEIGHT, 55 KGM			OCTOBER, 1925— WEIGHT, 66 KGM			FEBRUARY 1926 WEIGHT, 66 KGM		
Carbohydrate	Protein	Fat	Chloride	“G”**	Urine		Blood sugar	Urine		Blood sugar	Urine		Blood sugar
					Sugar	N		Sugar	N		Sugar	N	
grams	grams	grams		grams	grams	grams	per cent	grams	grams	per cent	grams	grams	per cent
60	48	156	1,836	103	0.7	9.5	0.16	0.6		0.19	0.7	8.6	0.20
145	67	161	2,297	200	38.4	10.3	0.26	14.8	8.4		1.2	7.9	0.20
231	86	199	3,059	301	118.0	10.3	0.29				17.6	8.6	0.25
346	67	158	3,074	400							83.9	9.3	0.35
Basal metabolic rate					+8			+11			-17, -9, +17*		
Respiratory quotient					0.81			0.80			0.71, 0.78, 0.76*		

\* On diets with “G” 103, 200 and 400, respectively

\*\* “G” =  $C + 0.58P + 0.1F$  (68)

Radiographic studies of the bones of the extremities showed no striking change except that the phalanges were somewhat wider than normal for their length. Stereoscopic films of the sella turcica showed an enlargement of the fossa more on one side than the other, so that the anterior clinoid process deviated upward and the floor was deeper on this side. The posterior clinoid processes were not sharply defined on either side. There was x-ray evidence of a small stone in the right kidney pelvis.

The blood Wassermann reaction was negative and the red and white blood counts, hemoglobin, blood pressure and stools were normal. The urine con-

TABLE 2

*Acromegaly diabetes* Effect of insulin on glucose and nitrogen excretion and fasting blood sugar concentration Daily diet throughout period of study contained carbohydrate 145 grams, protein 67 grams, fat 161 grams and introduced 200 grams glucose ("G," Wood, alt) (68) into the body

DATE 1925	URINE			BLOOD SUGAR	INSULIN
	Volume	Sugar	N		
	cc	grams	grams	per cent	units
March 18					
March 19	2,320	37.8	10.6	0.26	
March 19					
March 20	1,890	33.5	10.6	0.27	
March 20					
March 21	1,865	46.6	10.5	0.26	
March 21					
March 22	1,630	35.6	9.3		
March 22					
March 23	1,180	17.0	8.9		50
March 23					
March 24	1,240	20.2	9.4	0.25	50
March 24					
March 25	1,430	16.1	10.1	0.25	50
March 25					
March 26	1,370	15.3	7.9	0.24	90
March 26					
March 27	1,520	14.4	8.7	0.22	90
March 27					
March 28	1,880	10.9	10.4	0.21	90
March 28					
March 29	1,260	2.3	6.8		90
March 29					
March 30	1,830	5.7	9.9	0.19	90
March 30					
March 31	3,040	2.1	10.3	0.20	90



tained sugar, which was identified as glucose, and occasionally erythrocytes and albumin

Three metabolic studies were conducted at approximately six-month intervals during the period of a year in which this patient was under observation. Table 1 contains a summary of the quantitative findings obtained in these studies. Each diet was allowed to continue from four to ten days until the daily blood and urine findings became constant. The figures in the table represent the averages of these constant daily findings on each diet. Table 2 contains the results of a study of the effect of insulin on the urinary glucose and nitrogen excretions and the fasting blood sugar concentration. In this table the results are recorded by twenty-four-hour periods. Urinary sugar was estimated by the method of Folin and Berglund (69), blood sugar by that of Folin and Wu (70), and nitrogen by Kjeldahl. Eli Lilly & Co.letin (U-40) was the insulin preparation used.

*Comment.* An analysis of the information obtained in the foregoing study of this case of acromegaly discloses the following facts:

1. The acromegaly appeared when the patient was twenty-six years old and had existed from two to three years when studied. It was associated with a renal calculus and diabetes mellitus.

2. That a tumor of the pituitary gland existed was indicated by radiographic studies. The headaches were the only sign that the tumor exerted pressure upon the surrounding structures. There was no clinical evidence of regional involvement of the central nervous system unless the diabetes may be considered to be a sign of this.

3. The diabetes appeared in the third year of the acromegaly. It answered the description of ordinary diabetes mellitus in almost all respects, namely,

- a. Thirst and polyuria accompanied the presumably heavy glycosuria at the onset of the diabetes and disappeared when the glycosuria was reduced by suitable dietetic management.

- b. There was no abnormal glucose excretion when the glucose supply was low. When the supply was increased above a certain level a glycosuria occurred which remained constant as long as the supply was constant. As the supply was increased the excretion increased absolutely and also relatively until nearly 100 per cent of the last diet increment appeared in the urine (table 1).

- c. A constant glucose excretion which occurred while the supply

was constant was substantially reduced by the administration of insulin subcutaneously. A corresponding reduction of the fasting blood sugar concentration was observed. The nitrogen excretion was not materially changed (table 2).

4. A diet with a daily glucose value<sup>2</sup> of 200 grams which originally resulted in a daily glucose excretion of 38 grams caused but 1 gram to be excreted a year later, and correspondingly the glycosuria resulting from the ingestion of a diet of 300 "G" dropped in the year from 118 to 18 grams. In other words the patient's ability to utilize glucose or "tolerance for sugar" was observed to improve significantly within a year.

It may be remarked that during the period in which this change occurred the hypophysis was subjected to roentgen ray therapy weekly for three months, the patient gained 25 pounds in weight, and the basal metabolic rate was essentially unchanged.

5. No consistent variability of the glycosuria from day to day was observed when the food intake was maintained at a constant level.

In this case, therefore, we have quantitative evidence that *the diabetes of acromegaly at any one time behaves like an ordinary diabetes mellitus*. However in the course of the acromegaly the diabetes may run an unusual course in that it may show a spontaneous tendency to become milder or to disappear.

#### *Diabetes in pituitary disease without acromegaly*

It has been pointed out that acromegaly is the important clinical field for study of the relation of the hypophysis to diabetes, as tumor or hyperplasia of the hypophysis almost invariably exists and diabetes or glycosuria is commonly associated. Various other disorders of the hypophysis without acromegaly (hypoplasia, atrophy, tumor, cyst, syphilis, tuberculosis, abscess, hemorrhage) also not uncommonly occur, however, and the gland is often secondarily involved by pressure or extension of similar lesions in its vicinity. These conditions afford another medium for study of this problem.

Glycosuria and diabetes have been said to be very infrequent in non-acromegalic disorders of the hypophysis as contrasted with their fre-

<sup>2</sup>  $C + 0.58 P + 0.11 F = "G"$  (68)

quency in acromegaly Borchardt stated that he found no instance of glycosuria in a study of the cases of disease of and in the region of the hypophysis reported in the literature from 1886 to 1908 (12) In 1909 Frankl-Hochwart observed glycosuria only twice in a study of hypophyseal and juxta-hypophyseal disease without acromegaly (71), and states (p 110) "Die bei Akromegalie so häufig beobachtete Zuckerausscheidung ist bei unseren Fällen nur ganz vereinzelt beobachtet worden" In Rhein's collection of 169 cases of pituitary tumor (including 52 with acromegaly) glycosuria occurred 7 times, but the author does not state how many of those with glycosuria were acromegalic (72) Kollarits collected 51 cases of pituitary tumor without acromegaly from the literature and appended 2 such cases of his own (73). He is said to have stated that glycosuria was not present in any of these cases (Borchardt, Anders and Jameson, Falta, Ott, Kraus, John) but the writer has found that Kollarits made no such statement in his paper His only reference to glycosuria is that the urine contained no sugar in the two appended cases of his own As a matter of fact, later studies have disclosed that the association of glycosuria with nonacromegalic disorders of the hypophysis is by no means as unusual as the earlier studies indicated In 1913 Sinton and Rol reported a case of juvenile diabetes, infantilism and tumor of the hypophysis (74) They were able to find in the literature 9 other cases of hypophysis disease without acromegaly accompanied by glycosuria The following year Anders and Jameson took issue with Borchardt and others concerning this particular point (19) They studied the literature for the period of five years (1908 to 1913) following Borchardt's bibliographic search, and found in all 183 cases of pituitary disease Eighty-eight were cases of acromegaly and glycosuria occurred in 16 of these, while in the remaining 95 with no acromegaly (or in several cases questionable acromegaly) glycosuria occurred 10 times In this series at least these figures indicate an inappreciable difference in the frequency of glycosuria in disease of the hypophysis with and without acromegaly Furthermore, in addition to these 18 cases separately collected by Sinton and Rol and Anders and Jameson, the writer has observed in the course of this study, incidentally and after no systematic search, 20 additional case reports by Grossman (75), Aufrecht (2 cases) (76), Steensma (77), Brugsch (78),

Weber (79), Brown (2 cases) (80), Verron (3 cases) (81), Bleibtrau (82), Lhermitte and Roeder (83), DeTeyssieu (84), Lhermette and Fumet (85), Kraus and Reisinger (3 cases) (28), Meineri (86) and Gibson (87), in which diabetes or glycosuria accompanied non-acromegalic disorders of or near the hypophysis. The existence of the parhypophyseal lesion was demonstrated by good clinical evidence in the cases of Steensma, Brugsch, Bleibtrau, DeTeyssieu, Lhermitte and Fumet, Meineri and Gibson, and by post mortem examination in all the others. This total of 38 cases of this type compares favorably with the estimated total of 130 cases of acromegaly with diabetes or glycosuria reported in the literature of the same period.

### *"Hypophyseal diabetes"*

There are a few scattered references to a hypophyseal type of diabetes which have not been mentioned in the foregoing consideration of diabetes in acromegaly and other types of clearly demonstrable pituitary disease. Brugsch described 4 cases which he considered to be hypophyseal diabetes (78), although in only one of them were there signs of a hypophyseal lesion (good clinical evidence of a syphilitic basilar meningitis). This patient excreted 3 to 6 liters of urine daily containing glucose in a concentration not exceeding 0.5 per cent and the glucose excretion did not appear to vary even though appreciable changes were made in the quantity of carbohydrate ingested. The other 3 cases reported by Brugsch presented no evidence of pituitary disease but they showed in common with the first a slight glycosuria which was not much altered by changes in the diet, and a polyuria out of proportion to the glycosuria. The classification of these latter cases as hypophyseal diabetes merely because of these characteristics of polyuria and slight unvarying glycosuria in the absence of any sign of pituitary disease would seem to be questionable. However, the first case in which disease in the region of the pituitary was demonstrated is instructive and may be cited as an instance of disease of the hypophysis without acromegaly associated with glycosuria.

Koopman reported 2 cases which he called hypophyseal diabetes (23), because the administration of hypophysis tablets by mouth appeared to enable the patients to eat more food (especially meat) than formerly. There was no sign of hypophyseal disease in

either case. Many of his other cases of diabetes showed no response to hypophysis extract. Steensma (77) gave a brief description of a young girl with diabetes and x-ray evidence of a pituitary lesion who seemed to develop a higher tolerance for carbohydrate after the administration of hypophysis tablets by mouth. He stated that he has observed a similar effect in other cases of ordinary diabetes. Variations in the apparent tolerance are common in diabetes, and can hardly be attributed to hypophysis extract unless careful metabolic studies are conducted which would exclude emotional, infectious and often indeterminate factors affecting the tolerance. Labbé (22), Falta (89), Medigreceanu and Kristeller (88), and Bleibtrau (82) have each reported that the injection of pituitary extract had no effect upon the glycosuria in certain cases of acromegaly and pituitary tumor with diabetes.

### *Hypopituitarism and diabetes*

A discussion of the clinical facts concerning the relationship of the hypophysis and diabetes would not be complete without reference to that group of disorders considered to be due to a deficiency of pituitary secretion and called hypopituitarism, which are characterized chiefly by obesity, delayed development of sexual organs and functions, peculiarities of hair growth and distribution, retarded mental capacity, etc. Briefly, the conclusion that this condition is a result of a lack of pituitary secretion is based partly on the fact that in many of these cases a lesion of or near the hypophysis resulting in a loss of hypophysis substance has been demonstrated, and partly on the fact that the reproduction of similar conditions experimentally by hypophysis extirpation in animals is possible (particularly Aschner and Goetsch, Cushing and Jacobson). Practically all authors agree that this condition is rarely associated with glycosuria, but that, on the contrary, the usual finding is an increased tolerance for carbohydrates. After a thorough study of the literature, Rosenberger stated that he did not know of a single case of the type of clinical disorder known as Frohlich's syndrome in which glycosuria had been present (20). Von Noorden (90), Swale Vincent (91), Cushing (37), Hale-White (92), Froment (26), and Anders and Jameson (19), are some of the many authors who state that a deficiency of hypophysis secretion is

accompanied by an abnormally high alimentary tolerance for carbohydrates. Evidence for this is contained in studies by Goetsch, Cushing and Jacobson (16), Forsbach and Severin (93), Falta (89), and Bondi (94). Cushing has suggested, and many clinicians use, the observed alimentary tolerance for carbohydrates as a test for hypopituitarism, and the supposition that it is high in hypopituitarism is an important link in Cushing's chain of evidence for his theory that an increase of pituitary secretion leads to a diminished tolerance for carbohydrate, glycosuria or diabetes, while a decrease results in an abnormally high tolerance with increased conversion of sugar into fat and obesity, although Cushing has gone a step further and limited this function of the hypophysis to the posterior lobe.

Some doubt has been raised as to the legitimacy of the usual interpretation of this fact. Gibson's case (87) was a typical example of the disorder known as hypopituitarism, and there was x-ray evidence that the hypophysis must have been very small if not absent, yet diabetes was present. In some of the other cases of non-acromegalic pituitary disease mentioned above the hypophysis was found at necropsy to be greatly diminished in size. John reported 5 cases of clinical hypopituitarism with glycosuria or the type of blood sugar curve following oral glucose administration which would suggest decreased carbohydrate tolerance (95). Of 3 other cases he studied " which had the typical clinical symptoms of the disorder " the blood sugar curve following the ingestion of glucose was in 2 cases " of the type which denotes increased carbohydrate tolerance " and in the third " a type we get in normal individuals, and yet this patient had the most typical case of hypopituitarism in this group, showing all the signs of pituitary dysfunction " None of these 8 cases had local signs of a diminution of pituitary substance.

Finally in this connection, Wilder and Sansum giving glucose intravenously continuously and at constant rates in 2 cases of dyspituitarism showing the Frohlich syndrome (96), found that when an administration rate of approximately 0.8 gram glucose per kilogram per hour was exceeded, glycosuria occurred (as determined by a qualitative test). They observed essentially the same assimilation

lation limit in their 4 normal controls. In 3 cases with pancreas disease in which diabetes existed and in 5 cases of exophthalmic goiter, glycosuria appeared at lower injection rates, and the degree of reduction of the assimilation limit measured in this way was roughly proportional to the apparent clinical severity of the disease in each case. These authors concluded that as their patients with hypopituitarism behaved like normal individuals in respect of their ability to utilize glucose, the high tolerance reported by investigators using the oral method was possibly due to some other factor. The studies of Wilder and Sansum require confirmation in a longer series of cases.

#### EXPERIMENTAL FACTS CONCERNING THE RÔLE OF THE HYPOPHYSIS IN CARBOHYDRATE METABOLISM

This problem has been studied experimentally with animals by noting the results of hypophysectomy, administration of pituitary extract, stimulation of and the production of lesions in the hypophysis and central nervous system, and recently by pharmacological studies of the relation of hypophysis extract and insulin and the action of the latter in hypophysectomized animals.

##### *Operative manipulation of the hypophysis*

Caselli (1900) (99) and Friedmann and Maas (100) in the same year were apparently the first to observe that transient glycosuria frequently followed removal of the hypophysis in animals. This observation has been confirmed by practically all investigators working in this field, namely, Paulesco (101), Crowe, Cushing and Homans (102), Goetsch, Cushing and Jacobson (16), Handelsmann and Horsley (103), Aschner (104), Camus and Roussy (105), Bell (106), Sachs and MacDonald (44), and Dandy and Reichert (107). That this glycosuria is due to something other than the absence of the hypophysis was first demonstrated by Goetsch, Cushing and Jacobson, who found that any operative manipulation of the gland would frequently cause glycosuria (16).

Weed, Cushing and Goetsch (108), investigating this problem further, stated that they found in rabbits, cats and dogs under ether

anaesthesia, provided the liver contained sufficient glycogen, that direct mechanical or electrical stimulation of the hypophysis invariably produced glycosuria, and that glycosuria likewise followed mechanical or faradic stimulation of the superior cervical sympathetic ganglia. The latter procedure caused glycosuria even after section of all of the known nervous pathways to the viscera, namely, both cervical sympathetic trunks below the point of stimulation, both vagi, and the spinal cord at the level of the fourth thoracic vertebra (above the splanchnic outflow). In a single observation they noted no glycosuria on stimulation of the superior cervical ganglion in an animal previously deprived of the posterior lobe of the hypophysis, and reasoned that there was a sympathetic nervous control over the secretory function of the hypophysis, namely posterior lobe, stimulation of which caused glycosuria by means of a glycogenolytic substance liberated into the blood stream or cerebrospinal fluid. They maintained that the glycosuria must be due to a chemical agent and not to direct stimulation of the liver through nervous connections, because it occurred when presumably all nervous pathways to the viscera were severed, and did not occur when the posterior lobe was previously removed.

These results appeared to contribute confirmatory evidence to Cushing's theory that a posterior lobe hormone is responsible for the changes in carbohydrate metabolism occurring in disorders of the hypophysis, but they were not confirmed in subsequent studies by other investigators. Rabens and Lifschitz conducted similar experiments (109) and found that the ether anaesthesia itself produced in these animals a glycosuria which was not affected by superior cervical sympathetic ganglion stimulation, and furthermore, when stimulation was performed in conscious animals after the anaesthesia was ended and its attendant glycosuria had disappeared, no glycosuria resulted. Keeton and Becht (110, 111) failed to obtain hyperglycemia in dogs on electrical stimulation of the hypophysis when the splanchnics and the spinal cord at the second thoracic level were sectioned several days previously, thus contradicting other findings of Weed, Cushing and Goetsch, and recently Brugsch, Dresel and Lewy observed hypoglycemia on cervical sympathetic ganglion stimulation in dogs rather than hyperglycemia (112). These contradictory find-



ings obviously raise considerable question as to the permissibility of the interpretations of Weed, Cushing and Goetsch, especially when it is recalled that their critical experiment, in which no glycosuria was observed on sympathetic stimulation after posterior lobe removal, was the single positive experiment involving the hypophysis alone

Thus while it seems firmly established that stimulation or manipulation of the hypophysis is capable of causing an increase in the blood sugar concentration and glycosuria, it does not by any means appear certain that this is caused by the discharge of a glycogenolytic hormone from the hypophysis

More recently evidence has rapidly accumulated that this glycosuria which appears to be hypophyseal in origin, as well as other symptoms which have been attributed to a lack of hypophysis secretion such as delayed sexual development, retarded growth, adiposity and diabetes insipidus, are really due to lesions in the hypothalamic region in the floor of the third ventricle Aschner was the first to observe that glycosuria may be provoked by an injury in this region. In 1909 he demonstrated a 4 per cent glycosuria over a period of two days following a "hypothalamuszuckerstich" (113), and in 1912 in an extensive report of studies on the effect of hypophysis removal on sexual development, growth and life, he stated that glycosuria was practically always produced when the tuber cinereum was injured (104) Camus and Roussy paid particular attention to this region in their 195 hypophysectomies and piqures in dogs and cats (114), and although primarily concerned with diabetes insipidus, observed that in their few cases in which glycosuria occurred, this region of the brain was afterwards found to have been injured during the operation as a rule These authors are emphatic in their assertion that symptoms usually attributed to disorders of pituitary secretion are actually a result of brain lesions in the floor of the third ventricle, especially the tuber cinereum Bailey and Bremer, also interested chiefly in polyuria, frequently observed glycosuria following their punctures in this region (115), and favor Aschner's conception of a head ganglion of the visceral nervous system in the brain stem just above the hypophysis ("Stoffwechsel- und Eingeweide-centrum im Zwischenhirn"), injury of which is responsible for many of the symptoms usually attributed to hypophysis disorders Recently Camus, Gournay and LeGrand have

succeeded in producing in rabbits a prolonged glycosuria (in one case forty-seven days) of at times a severe grade (as high as 6.4 per cent) by injury of the tuber cinereum (116)

Sachs and MacDonald have performed convincing experiments in this connection (44). Glycosuria did not occur at all and there were no other marked symptoms after 11 total or partial hypophysectomies in which the base of the brain was carefully avoided at operation and found to have been uninjured by serial sections post mortem. In 16 other experiments the brain was purposely or accidentally injured during the hypophysectomy. Eight of these animals died within twenty-four hours and the other 8 in which the brain injury was less marked showed symptoms of glycosuria, polyuria, lethargy and emaciation, a definite contrast to that group in which the hypophysis was removed and brain injury carefully avoided. Hypothalamic puncture without hypophysis removal was performed in 5 other animals, and this was followed as a rule by symptoms, including glycosuria, similar to those which occurred in the animals which suffered hypothalamic injury as well as hypophysectomy. In other words, they found that few symptoms followed hypophysectomy alone, while injury of the floor of the third ventricle, with or without hypophysectomy, caused marked disturbances, including glycosuria.

Certainly, at any rate, it may be accepted that transient glycosuria frequently follows manipulation of the hypophysis or its adjacent structures. The transient nature of this glycosuria and the fact that it is less likely to occur in animals previously starved has often been taken to suggest that it is due to a temporary rise in the rate of glucose supply above the assimilation limit due to an increased rate of glycogenolysis. Whether the increased glycogenolysis is due to nervous influences acting on the glycogen reservoirs or to a chemical action of hypophysis secretion cannot be determined from the experimental data in hand. It should also be borne in mind that the phenomenon could be explained fully as well on the basis of a temporary check on the rate of insulin secretion from the islet apparatus in the pancreas, and that this region of the brain may possibly contain a center which controls this function. This view would be in opposition to that commonly entertained concerning the mechanism of *piqure* glycosuria. But it is not impossible that the

current conception based on work that is now ancient is in need of revision and that piqûre glycosuria and diabetes are more closely related than has been maintained since the time of Claude Bernard

*Carbohydrate tolerance following hypophysectomy*

Goetsch, Cushing and Jacobson are responsible for the view that extirpation of the hypophysis eventually leads to an increased tolerance for carbohydrates. In the course of their elaborate studies on hypophysectomized dogs reported in 1911 (16) they determined the smallest amount of sugar given orally in a single dose which would cause the urine to show a positive reaction for sugar by the ordinary qualitative reducing tests, before and after nearly total removal of the hypophysis or of either lobe alone. They considered this to be a measure of the alimentary tolerance and found that after posterior lobe removal there was an immediate temporary reduction of the tolerance estimated in this way but that later there was a gradual increase above the preoperative level—as much as 60 per cent in some cases, and that this apparent increase in tolerance often occurred simultaneously with adiposity and was reduced by anterior or posterior lobe administration. Anterior lobe removal caused no appreciable change in tolerance. As these findings are similar to those which these investigators obtained in their clinical studies in various types of pituitary disorders they were considered to justify the conclusion that an increase of posterior lobe secretion causes a diminished tolerance for carbohydrates, glycosuria or diabetes, while a diminished secretion leads to an augmentation of tolerance.

Sachs and MacDonald conducted somewhat similar studies in some of their hypophysectomized dogs and found that 9 animals from which the posterior lobe was removed alone or together with the anterior lobe showed postoperatively “a delayed rise in the blood sugar curve after glucose administration” (0.5 gram glucose per kilogram per mouth), while 2 other dogs from which the anterior lobe alone was removed showed a normal curve. A normal curve was considered to be one whose peak occurs one-half hour after glucose administration instead of one hour as was observed in their animals showing the delayed rise.

These authors, as well as Allen and Bailey, have suggested that a

determination of the intravenous assimilation limit for glucose in hypophysectomized animals would be of value. A search of the literature has disclosed but three brief references to experiments of this nature. In his discussion of the paper of Sachs and MacDonald, Bailey stated that with Berglund he studied the carbohydrate tolerance after hypophysectomy in dogs by means of intravenous glucose injections and found that it apparently did not vary from the normal, although it was so variable in normal animals that the studies were not considered to be significant (117). Allen described an experiment (118) in which Pratt administered glucose subcutaneously to a dog hypophysectomized by Homans (unpublished). The tolerance estimated in this way was only 2 grams per kilogram, which was said to be one-fourth normal. Houssay, Hug and Malamud briefly state (119) that intravenous injection of glucose into dogs at a rate of 1 gram per hour for one and one-half hours gave hyperglycemia curves which were similar in normal and hypophysectomized dogs. They concluded that hypophysis removal results in no augmentation of the tolerance for carbohydrates. Thus, the conclusion that a lack of hypophysis secretion results in an increased tolerance for carbohydrates seems to be based so far as direct experiments are concerned entirely on alimentary determinations the significance of which may be open to considerable question.

Evidence for the view that hypophysis extirpation does not alter the carbohydrate tolerance is contained in the results of the following experiment conducted by G. M. Curtis and the writer.

The animal used was a female dog from which the hypophysis had been removed by the sphenoidal route eighteen months previously by Curtis in the course of his studies on the experimental production of diabetes insipidus (120), and that the removal was complete was later verified by autopsy. The dog was in excellent physical condition and had shown no permanent constitutional disturbance as a result of the removal of the gland.

*Methods* No food for twenty-four hours prior to injection periods but water as desired. Glucose (recrystallized Corn Products Refining Co. C. P. dextrose) administered intravenously, continuously and at constant rates by means of the Woodyatt intravenous apparatus according to the method described by him (97). Length of injection

periods four hours, concentration of solution about 18 per cent Urine collected continuously by in-dwelling catheter during injection periods, diluted to 300 cc, and analyzed for sugar by Folin-Berglund method

The results of this experiment were as follows

INJECTION	WEIGHT OF DOG	GLUCOSE INJECTION				URINE EXCRETION	
		Concentration of solution	Volume of solution	Glucose injected	Rate per kilogram per hour	Volume	Glucose excreted
	<i>kgm</i>	<i>per cent</i>	<i>cc</i>	<i>grams</i>	<i>grams</i>	<i>cc</i>	<i>grams</i>
1	10 0	18 3	340 4	62 3	1 56	225	11 5
2	10 25	18 4	297 5	54 7	1 33	188	6 7

Length of injection periods in each experiment four hours

Thus it was found that when a hypophysectomized dog was given glucose intravenously at constant rates for four-hour periods, 62 3 grams representing an administration rate of 1 56 grams per kilogram per hour, caused a glucose excretion of 11 5 grams, and 54 7 grams at a rate of 1 33 grams per kilogram per hour, caused a glycosuria of 6 7 grams Unfortunately no data of this kind were obtained with this dog before the hypophysis was removed, but the following results obtained by Felsher and Woodyatt in normal dogs using identical methods may be cited for comparison (98)

DOG	GLUCOSE INJECTION PER KGM PER HOUR	GLUCOSE EXCRETION PER 10 KGM PER FOUR HOURS
	<i>grams</i>	<i>grams</i>
IV	1 1	5 8
I	1 2	4 3
II	1 2	7 2
III	1 3	0 2
III	1 4	0 2
III	1 5	2 4
VI	1 5	0 2
VI	1 8	1 4

From these experiments it may be seen that the administration of glucose intravenously into normal dogs at uniformly sustained rates comparable to those used in the present study caused glucose excretions in grams per four hours per 10 kgm (the weight of the animal used in the present experiment) of from 0 2 to 7 2 grams, while similar

rates of administration in the case of the hypophysectomized dog herein reported caused excretions of 6.7 and 11.5 grams per four hours per 10 kgm. This dog was accordingly not abnormal in respect of its ability to utilize glucose as measured in this manner.

*Glycosuria after hypophysis extract administration*

Most investigators have found that injection of extracts of the hypophysis may produce transitory hyperglycemia and glycosuria, although a few secured negative results (Giadovini and Ruggieri (121), Falta with Bernstein (122), Priestley (123), Newburgh and Nobel (124), and Carlson and Martin (125)). Borchardt was the first to record this finding (12), and confirmatory results have been obtained by Rossi (126), Franchini (127), Ott and Scott (128), Goetsch, Cushing and Jacobson (16), Miller and Lewis (129), Partos and Katz-Klein (130), Burn (131), Jacobson (132), Claude and Baudouin (133), Achard, Ribot and Binet (134), and Mochlig and Ainslee (135). The interpretation of this phenomenon is in dispute. The majority attribute it to a specific glycogenolytic action of the hypophysis extract (posterior lobe—Cushing). Franchini observed intestinal ulceration in the only 2 who showed glycosuria of 22 puppies injected, and felt that this was the cause of the glycosuria, as intestinal injury in man (for instance that caused by ingestion of lye or aqua regia) is capable of causing glycosuria (Zack). Miller and Lewis also believed that hypophysis extract has no specific effect on sugar metabolism, as intestinal disturbances, tremor and dyspnea, which also follow its administration, are of themselves sufficient to cause glycosuria (Gaultier, Minkowski, Underhill). Ott and Scott observed that this glycosuria which follows pituitary extract injection was prevented by section of the splanchnics and by thyroidectomy. Partos and Katz-Klein observed changes in the water content of the blood following the administration of the extract and felt that this was responsible for the conflicting results obtained by various investigators.

An interesting discussion has arisen as a result of the glycosuria-producing action of hypophysis extract. Cushing and Goetsch (136) found that the administration of concentrated cerebro-spinal fluid was followed by transient glycosuria and other physiological phenomena similar to those caused by posterior lobe extract injection. They

concluded from this and other studies that Herring's theory that the pituitary discharges its secretion directly into the cerebro-spinal fluid in the third ventricle by way of the infundibular stalk (137) was correct. This possibility was investigated further by Carlson and Martin (125), Levy and Boulud (138), Cow (139) and Dixon (140) with contradictory results, but Jacobson (132) obtained results similar to those of Cushing and Goetsch with an artificially prepared hypertonic solution chemically similar to the cerebro-spinal fluid concentrate used by the original investigators, which would appear to settle the question as far as the physiological action of cerebro-spinal fluid is concerned.

*Action of epinephrine and insulin in hypophysectomized animals,  
epinephrine, insulin and hypophysis extract*

Other pharmacologic studies have been conducted which are interesting in a consideration of the function of the hypophysis in carbohydrate metabolism. Stenstrom found that pituitrin inhibited the hyperglycemia due to epinephrine administration (141) and Burn obtained confirmatory results (142). Aschner investigated the glycosuric action of epinephrine in hypophysectomized dogs and concluded that it was less constant than in normal animals (104).

Recently a number of experiments have been performed which demonstrate the effect of hypophysis removal and extract administration on the action of insulin. In their experiments with decerebrate cats Olmsted and Logan found that they were unable to produce any substantial reduction of the blood sugar concentration in these animals by insulin administration. Investigating the reason for this they found that it was true only when the hypophysis was left intact, whereas when the hypophysis was removed with the cerebrum, insulin produced marked hypoglycemia and convulsions (143). Bulatao and Cannon repeated these experiments but were able to produce insulin hypoglycemia in decerebrate cats with the hypophysis preserved, and concluded that any abnormality in the observed action of insulin in hypophysectomized animals may well be due to injury of the hypothalamic centers which renders them functionally defective (144).

Houssay and Magenta reported that hypophysectomized dogs were more sensitive to insulin than normal (145). They injected insulin

in doses of  $1\frac{1}{2}$  units per kilogram into 5 normal and 5 hypophysectomized dogs and compared the effect by means of hourly blood sugar estimations and observations as to the occurrence of hypoglycemic symptoms. All of the hypophysectomized animals showed a marked lowering of the blood sugar concentration, and they all went into hypoglycemic convulsions and died four to fourteen hours after they received the insulin. All of the 5 controls survived the injections, none had convulsions, and the blood sugar concentration was reduced as a rule less markedly than in the other group, although the difference was not striking. Houssay, Mazzocco and Rietti (146) obtained similar results with toads. They also found, however, that the production of infundibular injuries in these animals led to the same increased sensitivity to insulin as hypophysis removal.

Finally, pituitary extract is capable of preventing and relieving insulin hypoglycemia and convulsions. This fact was first demonstrated by Burn (131) and has been confirmed by Magenta and Biasotti (147), Cammidge (148), Joachimoglu and Metz (149), Moehlig and Ainslee (135) and Lawrence and Hewlett (150). It was thought by some of these investigators that pituitary extract acts in a manner different from that of epinephrine in this respect because the glycogenolytic effect of pituitary extract alone as indicated by the slight rise in blood sugar following its administration appears of itself incapable of preventing the marked hypoglycemia of insulin. Others believe that the pituitary extract acts by mobilizing glycogen, as ergotamine, which prevents glycogenolysis, also prevents this antagonism of pituitary extract and insulin.

#### COMMENT AND RECAPITULATION

In the foregoing considerations there has been no attempt to discriminate between true diabetes mellitus and mere glycosuria accompanying those disorders of the hypophysis which are associated with disturbances of carbohydrate metabolism. In the field of animal experimentation the facts are easily summarized by the statement that true diabetes mellitus in the sense of a permanent impairment of the power to utilize glucose has never been reproduced by any experimental manipulation of the hypophysis or its surrounding structures, although a glycosuria of an appreciable magnitude may be provoked,



it has been invariably temporary and for this reason prolonged and accurate studies of the metabolism have not been forthcoming. In the clinical field disorders of carbohydrate metabolism are frequently encountered which vary widely from transient glycosuria induced only by ingestion of large amounts of carbohydrate to diabetes of a severe grade exhibiting all the characteristics of ordinary diabetes mellitus, running a rapid course and terminating in acidosis and death in coma. Of the total number of cases of acromegaly in which glycosuria has been observed (estimated at about 40 per cent) a number representing perhaps one-half have had other symptoms suggestive of diabetes such as polyuria and thirst and a small fraction of these cases have shown additional evidence such as denutrition and acidosis and death in coma to indicate that they were cases of truly outspoken diabetes mellitus. In many of the acromegalics, however, glycosuria has been the only sign of a disturbance of carbohydrate metabolism, and the same is true of perhaps a larger proportion of the cases of non-acromegalic disorders of the hypophysis, as Sachs and MacDonald and John have pointed out.

Therefore, in correlating the facts concerning the rôle of the hypophysis in carbohydrate metabolism it is necessary to decide whether these temporary or intermittent glycosurias have the same origin and therefore the same physiological significance as true diabetes mellitus. The transient glycosuria which may be induced by various types of hypophysis and central nervous system manipulation, trauma, new growths and other lesions is ordinarily thought to be due to an excessive rate of glycogenolysis which temporarily supplies glucose at a rate which exceeds the *normal* ability of the organism to dispose of it with the result that increased blood glucose concentration and glycosuria occur. The hyperglycemia and glycosuria exist as long as the glycogen and the stimulus to glycogenolysis endure. On the other hand the current conception of diabetes mellitus is that it is due to an absolute deficiency of insulin resulting in a subnormal capacity for utilizing glucose. In other words, while transient glycosuria induced by hypophysis and nervous system stimulation and the glycosuria occurring in diabetes mellitus are similar in that they are both due to a glucose supply rate which exceeds the glucose utilization rate then existing, they are considered to be due to essentially different

mechanisms in that in the former case there is no impairment of the ability to oxidize glucose and in the latter there is. It would seem altogether possible, however, that they are of similar origin, i.e., that the transient hyperglycemia and glycosuria provoked by piqûre or hypophyseal manipulation are really due to a temporary functional impairment of the insulin producing function, resulting in a temporary diabetic condition. Observations concerning the effect of piqûre glycosuria on the respiratory quotient would help to answer this question but these have not been recorded so far as the writer knows.

Thus, while it is possible that the transient glycosurias arising from hypophysis or central nervous system injury and the diabetes mellitus which so frequently accompanies hypophysis disease are entirely different in origin and should be considered separately in an analysis of the relation of the hypophysis to carbohydrate metabolism, it is also possible that they have the same origin and therefore the same physiological significance.

When the facts concerning the rôle of the hypophysis in carbohydrate metabolism are sifted and analyzed it is possible to recapitulate as follows:

1 Lesions involving the hypophysis or the portion of the brain adjacent to it, whether induced experimentally or occurring during the course of juxta-hypophyseal disease, are frequently accompanied by hyperglycemia, glycosuria or diabetes mellitus.

*a* A tumor of the hypophysis practically always exists in acromegaly and diabetic states are significantly frequent in this condition.

*b* Glycosuria and diabetes are by no means uncommon complications of other clinical disorders involving the region of the hypophysis.

*c* Glycosuria may be produced by experimental stimulation or injury of the hypophysis or the base of the brain in the region of the floors of the third and fourth ventricles. Glycosuria produced in this manner has been invariably temporary, i.e., no one has yet succeeded in producing permanent diabetes mellitus by experimental manipulation in the region of the hypophysis. It may be remarked in this connection that neither has anyone succeeded in experimentally producing a permanent or progressive lesion in the region of the hypophysis. Whether the presence of the hypophysis is necessary for the

production of glycosuria in this manner has not been determined. The most recent investigations indicate that the glycosuria which follows manipulation or stimulation of the hypophysis may be due to unavoidable stimulation or injury of the hypothalamus.

2 The diabetes mellitus which so frequently accompanies acromegaly resembles ordinary diabetes mellitus in all respects while it exists. It would seem to be justifiable, therefore, to conclude that it is a true diabetes mellitus due to a deficiency of insulin secretion from the islet apparatus in the pancreas.

3. The diabetes of acromegaly differs from ordinary diabetes without hypophysis disease in that it is capable of undergoing spontaneous temporary or permanent recovery. This fact is considered to be highly significant, for if the diabetes of acromegaly is a true diabetes and if it is capable of disappearing, then a knowledge of the mechanism involved might conceivably be employed in a study of the cause or cure of ordinary diabetes.

4 There is little reason to believe that a distinct hypophyseal diabetes occurs which is different from diabetes mellitus.

5 The belief that destruction or removal of the hypophysis results in an abnormally high power to utilize glucose which is the converse of diabetes mellitus is based largely on evidence derived from alimentary determinations of the tolerance for carbohydrates. These determinations are unreliable as they involve variable factors and are known to be subject to wide normal fluctuations. More reliable methods of measuring the functional glucose utilizing ability of the organism suggest that the removal of the hypophysis causes no permanent deviation from the normal.

6 The subcutaneous or intravenous administration of pituitary extracts is often followed among other things by transient hyperglycemia and glycosuria. A durable diabetic state has not been produced by hypophysis extract administration. The hypoglycemia and shock resulting from insulin administration in animals are relieved by hypophysis extract. In possessing these physiological properties hypophysis and suprarenal extracts are similar.

7 Hypophysectomized animals appear to be more sensitive to the action of insulin than normal, but the same sensitivity has been observed after hypothalamic injury in animals with intact hypophyses.

Thus, when the facts which constitute our present knowledge are collected and analyzed it is found that the chief reason for believing that as a gland of internal secretion the hypophysis is involved in the production of diabetes is that the administration of its extract, like epinephrine, may produce hyperglycemia and glycosuria and annul insulin effects. The importance of this fact becomes minimized when it is recalled that numerous other substances may produce hyperglycemia and glycosuria directly or indirectly through other physiological actions, and that the continuous administration of hypophysis extract is incapable of producing diabetes mellitus. Moreover, it is obviously hazardous to reason that because an extract of a given gland possesses a certain physiological property therefore the production of this effect is one of the functions of this gland during life. As Swale Vincent pertinently points out, the extract of a steer's hypophysis will cause uterine contractions.

All other facts which contribute to our present knowledge of this subject would seem to speak against the theory that the hypophysis by means of an internal secretion product influences the metabolism of carbohydrates or as a ductless gland is involved in the production of diabetes mellitus. Evidence seems to be accumulating to indicate that the hypophysis or hypothalamus or both contain nerve centers or tracts, the manipulation of which leads to alterations in the normal mechanism of carbohydrate combustion and storage.

#### CONCLUSION

The role of the hypophysis in carbohydrate metabolism is not definable with certainty at the present time. It is probable that it is without significance in this field as a gland of internal secretion, but that important nerve centers or pathways are situated in or near it which are concerned in the control of the metabolism of carbohydrates. It is not impossible that these centers or tracts are involved in the control of insulin secretion.

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# OBSTETRICAL INJURIES OF THE SPINAL CORD<sup>1</sup>

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## INTRODUCTION

Injuries of the brachial plexus and of the spinal cord, due to obstetrical accidents, are worth investigation from three points of view. First, they furnish material for the study of physiological disturbances, uncomplicated by gross injury of the skeleton or by disease. Second, the problems of treatment and of prognosis demand careful consideration. Third, we believe that almost without exception, injuries of the cord or plexus are due to unphysiological forces imposed upon the foetus. If this point of view can be supported by evidence, it is obvious that a definite obstetrical problem is presented.

Several factors have led to a concentration of children with birth injuries at the Children's Hospital. For many years a special clinic has been devoted to the care of these children and efforts have been made to start observation and treatment at the earliest possible moment. Moreover, the hospital has been selected by the Harvard Infantile Paralysis Commission as headquarters for the study of cases of poliomyelitis in children. In addition, the presence in Boston of Dr. Harvey Cushing's group has attracted a considerable group of patients with birth trauma, some of whom have been transferred to us. Clearly statistics from such a clinic will show an unusual proportion of cases with serious neurological injury.

The ordinary type of brachial palsy seems to us to be well understood. It is produced by traction, usually lateral, and in general is

<sup>1</sup> This paper was read in abstract at the 1925 meeting of the American Pediatric Association.

The publication of this paper was rendered possible by a grant from the Department of Pediatrics, Harvard Medical School.

characterized by paralysis of definite groups of muscles With the uncomplicated brachial palsies we are not concerned in this paper, nor will we consider palsies due to injuries of the phrenic nerves

However, in a surprising number of cases where the most obvious disability is paralysis of an arm, critical study produces evidence that the central nervous system is also involved In this paper only cases showing signs of cord injury, alone or in combination with plexus damage, will be discussed

The literature is extraordinarily difficult to collect and to summarize In the first place its collection involves search in the special journals of obstetrics, pathology, orthopedics and neurology The cases on the whole are not fully reported and unquestionably we have missed many pertinent papers On the other hand, no text-books give any adequate idea of the condition in which we are interested so that there is no established level of common knowledge from which to start We have placed a brief summary of the articles that seem pertinent in a later section

Certain general statements about the birth injuries may indicate our point of view In the first place we believe that any part of the nervous system can be injured by accidents during delivery Second, the result of intolerable stress upon any part of the foetus will be rupture of tissue Such injuries are necessarily diffuse and variable, structures being involved in accordance with their anatomical situation rather than their physiological function Third, the disturbances of function will not, on the whole, be progressive It seems to us that this conception of a diffuse, unselective and relatively fixed pathological condition is essential As a consequence of injuries of this type we get, of course, an almost infinite variety of physiological disturbances rather than a series of clean-cut syndromes In this paper we have confined our attention to lesions involving the cord below the phrenic nuclei, which lie about the level of the third cervical vertebra Obviously injuries at or above this level are of pathological rather than of clinical interest

The anatomic and physiologic units of the nervous system with which we are chiefly concerned are (1) the peripheral nerves, notably the brachial plexus, (2) the cervical sympathetic apparatus, and (3) the spinal cord

1 The brachial plexus is exposed to the danger of injury in every labor if traction is exerted. The manoeuvre of releasing a shoulder by lateral traction on the head must necessarily put the plexus on the stretch. Intolerable strain may do one of two things, either the cords of the plexus may suffer in any degree, from trivial and temporary injury due to stretching, to complete rupture, or the force may be transmitted along the nerve roots to the cord itself with consequent injury to that structure. In certain cases, notably in breech deliveries, both plexuses may be subjected to strain.

2 The cervical sympathetic fibres may be injured in various ways. Their integrity is threatened if the plexus injury extends to the lower roots near the spinal column and it is also possible that injury of the cord itself may involve interruption of fibres of the cervical sympathetic within that structure. Clearly, lower connections between the cord and the sympathetic can be involved at other levels by cord injury.

3 The relations of the spinal cord of the infant to surrounding tissues and the effect of obstetrical force upon it have been considered in detail in other papers. In a general way the facts seem to be as follows:

The spinal column of the infant consists of a series of elastic rings joined by relatively brittle discs and ligaments. Inside of the vertebral canal lies the tube of dura mater, attached by many strong fibrous bands in the cervical and lumbar regions, but very loosely attached to the surrounding canal in the thoracic region.

The cord itself is anchored firmly by the brachial plexus above and by the cauda equina below with but little support in the thoracic region. On the whole, it is relatively inelastic and friable. Obviously excessive elongation of the spinal column may put intolerable strain upon the cord or upon the meninges or upon both, between the 2 relatively stable anchorages. Also it is evident upon study of cadavers that lateral traction upon the head against a fixed shoulder, through tension upon the plexus, draws the cord to one side of the canal and fixes it there. Under these circumstances an increased pull, particularly if abrupt, may result in avulsion of the plexus from the cord. In addition to traction, hyperextension and torsion are forces to be considered. There is abundant evidence that fracture dislocations

in the cervical region are common. Clearly such injuries may or may not involve the central nervous system. Since most of these injuries are high enough to prevent the initiation of breathing if the cord is injured they are of relatively little importance in relation to the clinical disturbances to be considered.

In view of the fact that the lesions under review are diffuse, unselective and relatively fixed, it is obvious enough that the physiological pictures produced are varied and may duplicate those seen in congenital anomalies and in degenerative or infectious disease. In order to establish a presumption that a given case is due to birth injury we have required:

- 1 Evidence that the disability was noted as soon as an adequate examination was made. Unfortunately satisfactory reports of medical examinations were not always available and in certain cases we have felt justified in accepting lay evidence.

- 2 Evidence that such conditions as amyotonia, spina bifida, tumor, infection and so on were adequately considered.

- 3 Evidence that the disability was not progressive after the first days of life. Exceptions to this statement will be considered in connection with certain cases. Obviously contraction of scar tissue, infection and perhaps other causes may produce progressive disability.

- 4 Evidence that the forces imposed in labor might have produced the supposed injury. As will be at once noted on reading the reports we have frequently failed to obtain satisfactory obstetrical histories. This failure to obtain histories has not been due to lack of industry on our part. Furthermore, it is evident that no one except the obstetrician can possibly estimate the character and the intensity of the forces imposed. It is also apparent that the question whether the forces imposed were justified by obstetrical indications cannot be decided after the event. The reader must, therefore, keep constantly in mind the fact that no obstetrician ever uses what in his judgment is unjustifiable force and that in but few cases here reported it is suggested that delivery was not conducted in a manner sanctioned by tradition. The question whether obstetrical teaching is based upon adequate study of the effect of imposed force is, of course, another and wholly different question.

The diagnostic signs upon which we have relied to establish the

spinal origin of the disturbances under review have been largely physiological in nature. It is, of course, impossible to isolate and evaluate the various types of sensory disturbance in small children and the chaotic state of the conventional neurologic reflexes in infants prevents the drawing of valid conclusions from unusual manifestations on stroking the sole, tapping tendons and so on. On the other hand, it is to workers in laboratories that we owe most of our understanding of the nervous system and the method of these investigators has been the study of the effect of mutilations of the nervous system by recording behavior. On the whole, we believe babies can be studied by such methods with satisfactory results. We have, therefore, considered our material from this point of view.

The contributions of most interest are those of Head and Riddoch. The work of these investigators upon war wounds of the spinal cord furnishes an adequate background. In general they proved that transections above the lumbar enlargement did not necessarily, or indeed usually, abolish reflex activity of the isolated portion of the cord. This observation alone is of the utmost importance for it clears away a mass of tradition and misinterpretation. Naturally until the enormous material of the war was surveyed the neurologist had seen few cases of transection uncomplicated by sepsis, tumor or gross skeletal trauma. In most of the earlier cases complicating disease or injury made it difficult to study clean-cut abnormalities of the function of the cord. It is now evident, however, that reflex activity of the isolated cord is to be expected in man as well as in the laboratory animal.

With this information available it is possible and profitable to compare clinical cases with laboratory preparations. In a clinical paper it is not possible to review in detail the almost unlimited physiological possibilities but in general, after transection, it is possible to get many complicated reflexes, most of them flexor in type. Obviously in incomplete injuries spasticity, flaccidity, ataxia, total or partial anesthesia, and so on can be found in almost any combination.

In going over the cases, various possible methods of classification occurred to us. In view of the fact that any level of this cord may suffer in any degree it is clear that no series of discrete syndromes will be produced. With the meager obstetrical details available no

etiological classification is possible. On the whole it seems to us that the clearest method is to report in some detail typical cases, using photographs or diagrams or both if they seem helpful. As a matter of convenience the more severe cases will be reported first.

This method, particularly the diagrammatic explanations of the pathological condition, is subject to limitations. It is obvious, of course, that the diagrams are mere expressions of opinion. Furthermore, no attempt has been made to indicate degenerations of many of the tracts involved in a transection. We use certain terms rather loosely from a scientific standpoint but for purposes of this paper we have tried to use these terms consistently. We use *normal* in the sense that undamaged anterior horn cells are controlled by intact tracts from the brain as well as by intact afferent sensory tracts at the level under consideration. *Weakness* or *flaccidity* implies partial or total destruction, or at least physiological inertness, of anterior horn cells or peripheral nerves. *Spasticity* is used in the ordinary way. By *reflex activity* we mean the movements dependent on the integrity of isolated segments of the cord. *Sensory disturbances* are by no means easy to sort out in little children. We have had to be satisfied with more or less gross evidence of diminution or absence of pain in most instances. In some cases the presence of reflex activity complicated matters and in such cases we have had someone distract the attention of the child with food, toys or conversation while various stimuli were applied. Distress, rather than activity, was used as evidence of sensation of pain. Muscle sense, vibration and so on were investigated where possible. It is, of course, evident that the ordinary type of injury will not damage the posterior ganglion cells. If transient conditions cause pressure, it is quite probable that tracts will escape. With all the confusing elements due to the type of lesion and the age of our patients we have, on the whole, found that evidence of a fairly consistent sensory and motor correlation is available.

In considering the *bladder disturbances* and the occasional evidence of *sweating* over sharply defined areas, we made constant reference to Riddoch's paper. Any detailed discussion would involve us in controversy over physiological mechanisms beyond the scope of this paper and indeed beyond our knowledge. In a few cases we tried to follow out Riddoch's suggestions as to measurement of bladder pres-

sure. For various reasons we abandoned this line of study. For one thing it involved, we thought, some possibility of infection. The main reason, however, was that the results obtained in our early cases seemed to us so uncertain that reliable data would be hard to collect. Moreover, control experiments on uninjured babies would be needed. The attempt would, however, be of interest and we hope at a later time to investigate this problem.

With these various reservations due to the nature of our material as well as to our rather casual physiological training we present the following cases.

#### CASE REPORTS

The first 6 cases have been previously reported. Cases 1 to 5 were reported in 1923 by Crothers and case 6 by Ford in 1925. In all but one, recent examinations are reported. It is significant that *all* of Crothers' cases are still alive, their present ages being from 5 to 16 years. This fact alone suggests that early death is not the rule, provided the children survive the neonatal period.

*Case 1 Flaccid paraplegia with trophic ulcers.* J. B., now 5 years old, was seen at 2 weeks and has been under irregular observation since. The early history was reported by one of us in 1923 in the *American Journal of Medical Sciences*. The birth was a difficult extraction in a multipara. The child was completely flaccid and anesthetic below the costal margin, and the right arm was weak with diminished sensation. The pupils were equal. Lumbar puncture at the first visit revealed yellowish fluid with old blood. The sphincters, at first atonic, became automatic.

Since the first examinations, no essential change has taken place. The level of anesthesia has gone down a couple of inches, the condition now suggests that the brachial palsy was due primarily to peripheral injury as there is a zone of normally innervated thorax between the brachial region and the flaccid and anesthetic abdomen and legs. The child is perfectly intelligent. The sphincters after several years have again become incompetent and the child has developed severe and obstinate trophic ulcers. Gross and intractable contractures and deformities have developed under our eyes. Various attempts to control these, ranging from frames to surgical interference, have failed. Apparatus is now out of the question on account of the ulcers and, in any case with only one arm at all useful, crutches could not be used (figs. 1 and 2).



etiological classification is possible. On the whole it seems to us that the clearest method is to report in some detail typical cases, using photographs or diagrams or both if they seem helpful. As a matter of convenience the more severe cases will be reported first.

This method, particularly the diagrammatic explanations of the pathological condition, is subject to limitations. It is obvious, of course, that the diagrams are mere expressions of opinion. Furthermore, no attempt has been made to indicate degenerations of many of the tracts involved in a transection. We use certain terms rather loosely from a scientific standpoint but for purposes of this paper we have tried to use these terms consistently. We use *normal* in the sense that undamaged anterior horn cells are controlled by intact tracts from the brain as well as by intact afferent sensory tracts at the level under consideration. *Weakness* or *flaccidity* implies partial or total destruction, or at least physiological inertness, of anterior horn cells or peripheral nerves. *Spasticity* is used in the ordinary way. By *reflex activity* we mean the movements dependent on the integrity of isolated segments of the cord. *Sensory disturbances* are by no means easy to sort out in little children. We have had to be satisfied with more or less gross evidence of diminution or absence of pain in most instances. In some cases the presence of reflex activity complicated matters and in such cases we have had someone distract the attention of the child with food, toys or conversation while various stimuli were applied. Distress, rather than activity, was used as evidence of sensation of pain. Muscle sense, vibration and so on were investigated where possible. It is, of course, evident that the ordinary type of injury will not damage the posterior ganglion cells. If transient conditions cause pressure, it is quite probable that tracts will escape. With all the confusing elements due to the type of lesion and the age of our patients we have, on the whole, found that evidence of a fairly consistent sensory and motor correlation is available.

In considering the *bladder disturbances* and the occasional evidence of *sweating* over sharply defined areas, we made constant reference to Riddoch's paper. Any detailed discussion would involve us in controversy over physiological mechanisms beyond the scope of this paper and indeed beyond our knowledge. In a few cases we tried to follow out Riddoch's suggestions as to measurement of bladder pres-

sure For various reasons we abandoned this line of study For one thing it involved, we thought, some possibility of infection The main reason, however, was that the results obtained in our early cases seemed to us so uncertain that reliable data would be hard to collect Moreover, control experiments on uninjured babies would be needed The attempt would, however, be of interest and we hope at a later time to investigate this problem

With these various reservations due to the nature of our material as well as to our rather casual physiological training we present the following cases

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*Comment* This child illustrates well the severe type of cord injury. The experienced and skillful obstetrician used great force in order to deliver a baby whose life he regarded as in danger. The etiology of the trouble was almost absolutely established by early puncture. The forces involved evidently caused damage in a least two areas, first either in the cervical cord or in the brachial plexus and second, a more extensive area extending down from the lower thoracic region. The period of automatic control of the sphincters passed, apparently

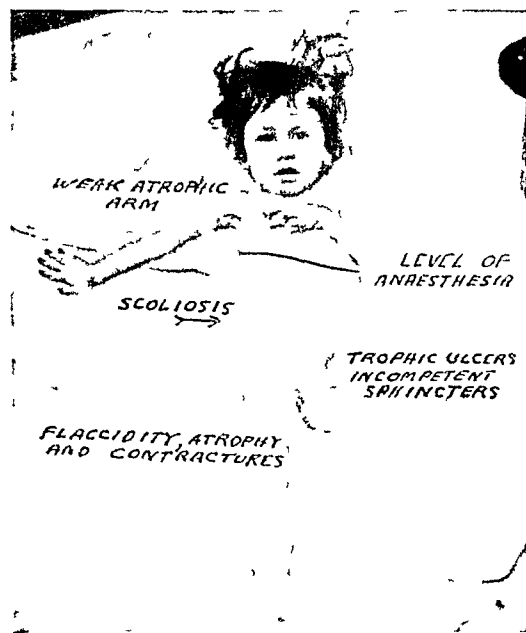


FIG 1 CASE 1 AT 4 YEARS

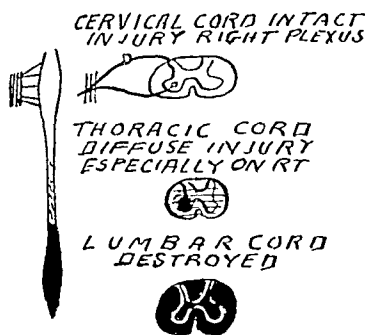


FIG 2 CASE 1 AT 4 YEARS

permanently, with the beginning of the trophic ulcers. This situation is quite in accordance with the observations of Head and Riddoch who record that reflex activity may subside if serious infection occurs. Further evidence on this point is contained in papers by Orr and Rows, who show experimentally that infection near a nerve can damage the spinal cord. In any case the unfortunate child has now a complete flaccid paraplegia with anesthesia, a handicapped right arm, incontinence of urine and feces, severe ulcers which are not cleared up by constant care, and obstinate and recurring deformities which cannot be handled on account of the poor condition of the skin.

*Note* Photographs of this case and of case 14 are reproduced from B Crothers' "Disorders of the Nervous System" 1926, by permission of D Appleton Company

*Case 2 Almost complete transection Persistent reflex activity Slight and temporary voluntary activity* F Y, a girl of 3 years, was first seen on the Orthopedic Service in 1921 The early history was reported by one of us in 1923 Briefly, when first seen, she showed a flaccid abdomen with

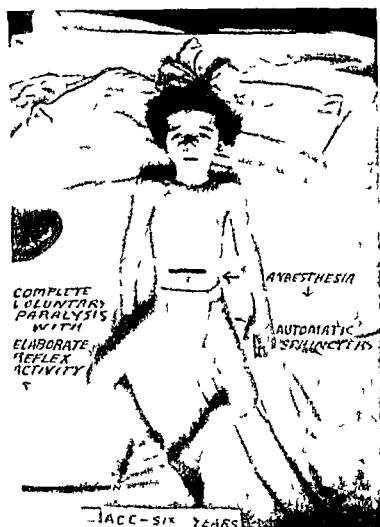


FIG 3 CASE 2 AT 6 YEARS

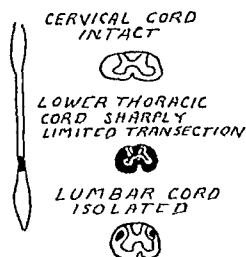


FIG 4 CASE 2 AT 6 YEARS

striking reflex activity of the legs and automatic sphincters with anesthesia below the navel A year later slight voluntary activity of the legs was observed and consciousness of micturition and defecation with some appreciation of pain over the legs was recorded The difficult version and extraction was a part of an accouchement force performed in the interests of the nephritic mother at the eighth month Three previous pregnancies ended normally

The subsequent history is interesting In the first place, the child gets about with long braces Second, no contractures have complicated the

He was the first child. The vivid description given by a neighbor, who was one of the 4 women holding the mother against the pull of the operator, left no question in our minds that force incident to difficult breech extraction could be logically held responsible for the paraplegia for which he was brought to us. Just before delivery a sudden snap was heard. The infant was apparently dead, but without efforts at resuscitation soon began to breathe and within a few hours to cry.

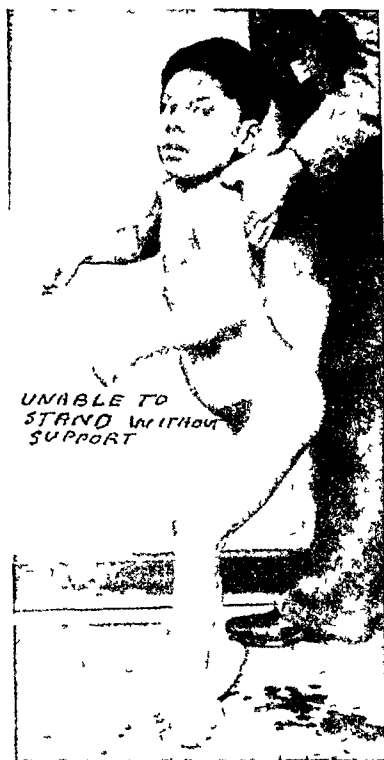


FIG 6 CASE 4 AT 6 YEARS

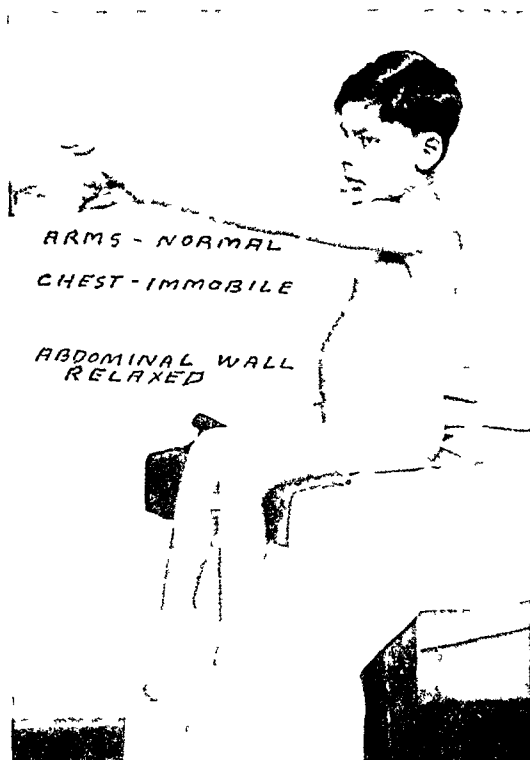


FIG 7 CASE 4 AT 6 YEARS

Paraplegia was observed at once. The early history of the case is like several others of this series, anesthesia below the nipples, flaccid trunk, and almost toneless legs with reflex activity.

We lost sight of the child a few months afterwards and did not see him again until April 14, 1926. He was then large for his age (6 years), in good general health, and competent mentally (figs 6, 7, 8, 9, 10).

He was still helpless below the chest. He could not sit without holding himself up by his hands. He collapsed in a heap if placed on his feet.

The details of examination are of some interest.

*Motor* The head, neck, and upper chest were normal. The lower chest moved poorly, if at all. Respiration was essentially diaphragmatic. The upper half of the abdominal wall was not entirely toneless. Below a line about one inch above the navel there was no tone at all. No abdominal reflexes nor cremasteric reflexes were elicited.

The legs lay extended and adducted. No voluntary movement whatever could be observed. On gentle handling it was obvious that the adductors were a little tight and the posterior muscles of the lower leg were stiff with rigid contractures of both Achilles tendons.



FIG 8 CASE 4 AT 6 YEARS

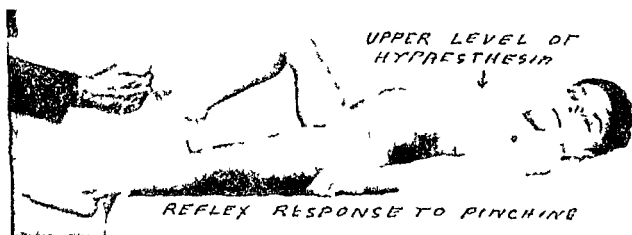


FIG 9 CASE 4 AT 6 YEARS

On more vigorous handling a very elaborate series of reflex activities could be set in motion. On pinching or pricking either leg a sharp homolateral flexion, spreading at times to the other leg, was seen. The receptive field for this reflex extended almost to the umbilicus. On attempting to elicit clonus in the usual way by flexing the foot upon the leg, a powerful extensor movement of the whole leg was found, strong enough to move the child upon the table. This extensor thrust was constant and equal on the 2 sides.

When sitting with legs hanging over the edge of the table, or when held

by the shoulders and swung free of the floor, the legs seemed quite limp. With some difficulty the conventional reflexes could be brought out. Clonus, of a curious indiscriminate sort, was easily elicited at the knees but not at the ankle. On the whole the right knee jerk was of ordinary spastic type, while the left was pendulous and the leg gradually swung to a standstill. The contracted Achilles tendons blocked any manifestations of ankle clonus. The Babinski sign was positive.

The bladder was evidently small with occasional discharge of small

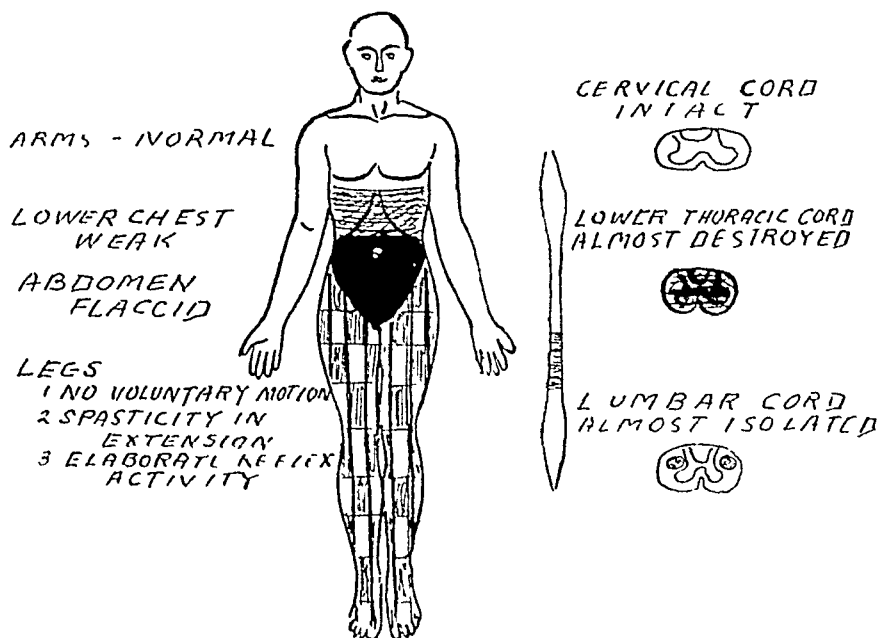


FIG 10 CASE 4 AT 6 YEARS

amounts of clear urine upon vigorous stimulation of the legs. The anus was not patulous. There were no bed sores. The urine was not infected.

*Sensation* was very difficult to study. The child spoke no English and the excitable Italian mother was by no means an easy assistant. Our impression was strong that no absolute anesthesia was present but that definite hypoaesthesia was present below the fifth rib increasing as we went down. Each prick or pinch or even stroke below the upper level of hypoaesthesia (the fifth rib) resulted in a red mark with a white elevation in the center. These startling manifestations were not as marked above the fifth rib. No sweating was elicited.



FIG. 11 CASE 5



*Comment* The original examination at 13 months was consistent with total physiological transection of the lower thoracic cord. The later examination shows the changes that may occur in such a case. This case illustrates the comparative value of two methods of approach. Any attempt to add up a collection of conventional neurological signs and fit this total into a described syndrome fails completely. On the other hand, if we think of the child as intelligent, with good arms, a weak trunk and legs practically severed from

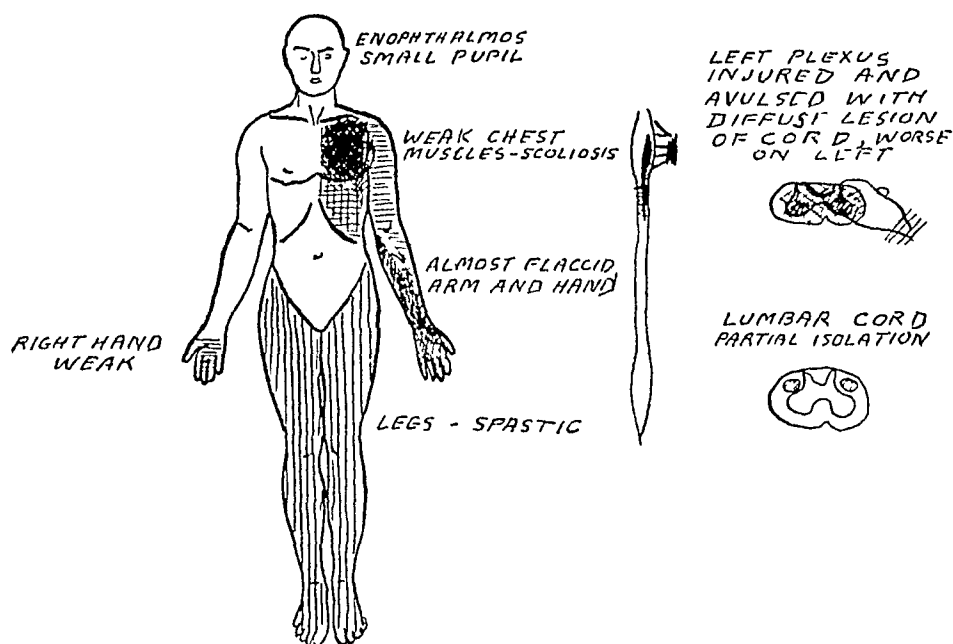


FIG 12 CASE 5

cerebral control we are in a position to suggest treatment. The physiological assets are intelligence and competent arms. On the wrong side of the ledger are the weak trunk and the isolated control of the legs. On the whole the reflex activity complicates rather than helps matters but the disadvantage of uncontrolled activity is balanced by the lack of trophic disorders in the skin.

We are therefore justified in correcting and preventing deformities and, by a combination of training and apparatus, attempting to get him on his feet. The problem is at least open to attack, if not to solution.

*Case 5 Brachial palsy Scoliosis Spastic paraplegia* E. H., a child of 12 years was seen by one of us in consultation in 1921. The details are reported in a previous article. She illustrates certain aspects of cord injury so well that we present the diagram and a skiagram, though we have no subsequent notes to offer, beyond a letter stating that her condition is essentially unchanged (figs 11 and 12).

The early history was of a primiparous breech labor with subsequent flaccid paralysis of the left arm, sympathetic paralysis shown by enophthalmos and small pupil, sensory changes, spastic paraplegia, and bladder disturbance.

*Comment* The most interesting point is the marked, sharply localized scoliosis. In spite of the evidence of severe plexus and cord injury the child is going to school, controls her sphincters fairly well and is, in general, an adequate person.

*Case 6 Destruction of lower cord Dislocation of spinal column Breech extraction* E. H. was seen by us in March, 1926, at the age of 22 months. An earlier examination at 6 months at the Johns Hopkins Hospital is recorded by Ford in the Archives of Neurology and Psychiatry in December, 1925.

The obstetrical story is clear and of great interest. The first pregnancy resulted in the death of a large baby (12 pounds at birth) with severe laceration of the mother. Four years later the mother again became pregnant. A consultant in another city advised careful regulation of diet and suggested that induction of labor might be considered later, or a Cæsarian section. The physician in charge did not feel that induction of labor was justifiable and was confident that pelvic delivery was possible. Labor started several weeks after the expected date. The mother had vigorous pains from three in the morning until eleven at night. The physician then ruptured the membranes and performed a version and extraction. According to the story given by the intelligent and reasonable father, some arrangement of cloth was fastened about the baby's groins and 2 men pulled together. Great traction was necessary to deliver the legs and body, the head offering little resistance. The birth weight was over 12 pounds. After delivery both mother and child "collapsed" and grave concern was felt about each. After respiration was established the baby seemed all right until several days later when examination revealed total paralysis of the legs.

The paralysis persisted, except for slight flexion at the right hip, followed at about 2 months by slight movement at the left hip.

When the child was examined at Johns Hopkins Hospital at six months, the following condition was recorded by Ford

"On examination the child seemed bright, alert and well developed for his age. The cranial nerves were normal. The arms moved freely, and the grips were strong. The child could hold his head up well, but could not sit up because of weakness of the lower extensors of the spine. Except for a feeble movement of flexion at the left hip when the child tried to crawl, no spontaneous movements of the legs were observed. Passive movements of the legs showed slightly diminished tone, but the muscles were of fairly good bulk and only slightly soft. The abdomen was bulging, and the abdominal muscles seemed flabby. An inguinal hernia was present on the



FIG 13 CASE 6



FIG 14 CASE 6

left. Respiration was diaphragmatic, and the lower ribs did not show any definite excursion on inspiration. There was a frequent discharge of small quantities of urine. Almost complete loss of cutaneous sensibility was found over the lower part of the body, but no definite level was demonstrated. The tendon reflexes were active in the legs, and ankle clonus could be elicited bilaterally. Plantar stimulation caused dorsal movement of the toes and flexion of all the other joints of the leg. This movement was strictly unilateral. The abdominal reflexes were not obtained. There were no trophic changes in the skin."

In addition the father states that evidence was found of dislocation of the twelfth thoracic vertebra upon the first lumbar and that operation was considered but decided against.

Since that time the child has developed mentally, talks freely, can sit alone and can drag himself about by his arms. The only incident of special interest was a fracture of the neck of the right femur. This was discovered and confirmed by x-ray examination in November, 1925. It was certainly post-natal as earlier skiagrams did not show it.

When we saw the child at 22 months the head, arms and chest were normal. The upper abdomen was weak but not totally paralyzed, the lower wall bulged, there was a small inguinal hernia on each side. The legs were essentially flaccid. On the right no motion, either reflex or voluntary, was made out. On the left there was fairly strong voluntary flexion and some adduction at the hip with contractures about the joint. No other movement was elicited. Electrical study showed no response to either galvanic or faradic current, except of the ilio-psoas on the left (figs 13, 14, 15 and 16).

Anesthesia was absolute below a line about 1 inch below the navel and hypoaesthesia was probable below the seventh rib.



FIG 15 CASE 6

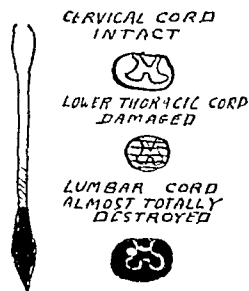


FIG 16 CASE 6

Urine was discharged, frequently with some force, at relatively short intervals. The bladder was not distended. The urine was clear, though a few motile bacilli could be seen in a fresh, clean specimen. The anus was patulous.

Lumbar puncture showed normal fluid with normal pressure phenomena.

Skinograms showed the same slip of the vertebrae which was noted at Johns Hopkins. New skinograms of the femurs showed essentially the same deformity as observed in those taken in November, 1925. The head was some distance from the shift, the acetabulum was atrophied. No union had occurred.

*Comment.* The case presents several features of interest. In regard to the obstetrical history, it is enough to tell the story. The evidence of adequate etiology seems conclusive. The exact pathological condition may be a matter for argument. The dislocation of the verte-

bral column is not much below the presumed site of the lesion. It is entirely possible that the vertebrae slipped across each other and injured the tip of the cord or at least the roots of the plexus. It is equally probable that the pull of the 2 men may have avulsed the cauda equina from the cord. In either case there is at present free flow of spinal fluid past the site of injury and in all probability no benefit would result from laminectomy.

The atrophy of bone in the legs is clearly seen in the skiagrams and can be assumed from the practically spontaneous fracture. No practicable method of improving the position or of hastening union occurred to us or to Dr P. D. Wilson, who saw the child with us. Apparatus is not well tolerated on limbs without nerve supply. Operation on atrophic bone seems unreasonable, furthermore in the presence of apparently permanent paralysis abnormal position is unimportant.

The fact that the child lost the lively reflexes and the other phenomena seen at 6 months is interesting. Our first impulse was to suppose tearing of membranes had led to dense adhesions about the lumbar enlargement. The free flow of fluid practically ruled out this possibility. Infection cannot be held responsible. In other cases regression of this sort, without adequate reasons being found, is noted. It is evident that the isolated cord is always likely to cease activity and in this case the damage was low, leaving relatively few units intact.

The photographs show the present status almost perfectly.

*Case 7 High physiological transection with death at four weeks. Minimal reflex activity. Autopsy.* M. S. was born by version and extraction and weighed 10 pounds. The operator, a competent obstetrician, met with great difficulty in the delivery. Resuscitation with oxygen was employed. Immediately after birth it was observed that the baby was completely paralyzed from the neck down.

The child lived for 4 weeks. During that time she appeared to be bright, moved her head actively and strongly, and showed no disturbance of the cranial nerves. Below the neck there was a flaccid paralysis, complete except for slight movement of the toes. Breathing was wholly abdominal. The intercostal and abdominal muscles were toneless. The arms lay extended at the sides and pronated. The legs were outwardly rotated and flexed at the hips and knees. No reflex activity could be elicited except of

the toes. Sensation was everywhere absent except over the head and neck (figs 17 and 18)

A clinical diagnosis was made of a hematomyelia of the cervical cord, probably due to fracture of the spine

At 4 weeks of age the child unexpectedly died

Autopsy confirmed the clinical diagnosis. The brain and its surrounding membranes showed no hemorrhage or other abnormality. The brachial

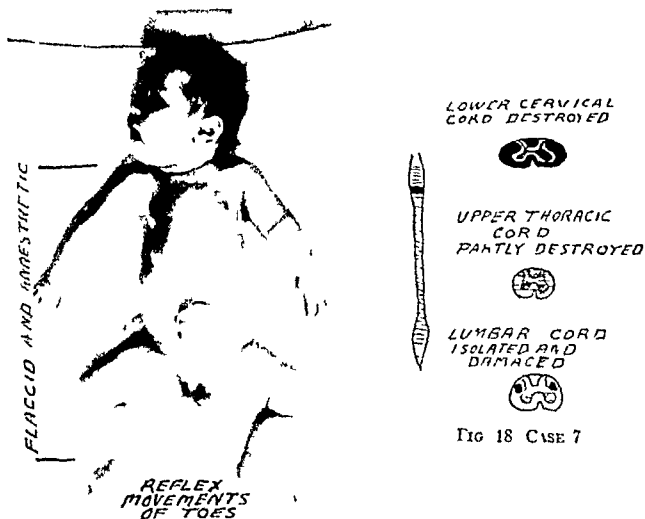


FIG 18 CASE 7

FIG 17 CASE 7

plexus on either side showed no trauma, but there was a fracture of the fifth cervical vertebra, involving the arch in 2 places and the body, with partial separation of the fragments but no displacement. The anterior common ligament of the vertebral column was ruptured at the same level. There was no evidence of hemorrhage into the meninges, but on section of the cord a fusiform hemorrhage was found in the postero lateral regions, extending from the sixth cervical to the fourth thoracic segments. Microscopic study showed vacuolization of the matrix of the anterior and lateral gray matter from the fourth cervical to the fourth thoracic segment, also, an encapsu-

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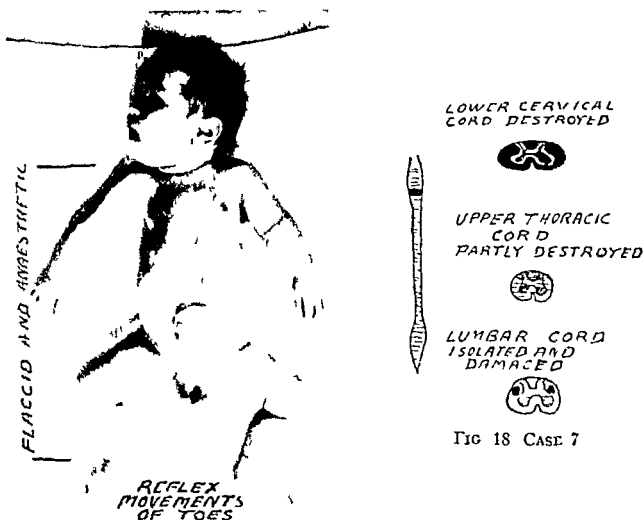


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lated mass of blood in the left posterior quadrant of the white matter with extensive loss of cord substance in the eighth cervical segment. No nerve cells were found in this segment. The anterior horn cells in all sections examined, including those of the lumbar segments, appeared granular with poorly staining nuclei.

*Comment* We have, then, fracture of the fifth cervical vertebra with gross hemorrhage extending through seven segments of cord substance and microscopic evidence of anterior horn cell disturbance throughout the entire cord. From the clinical standpoint the lesion amounted to complete transection of the cervical cord. Up to the time of death almost no reflex activity had been observed in the lower extremities.

This baby was delivered by conventional manoeuvres in a University clinic. Clearly a 10 pound breech baby presents a difficult problem. Clearly, too, the fracture revealed by the autopsy is sufficient evidence of the breakdown of the foetal tissues before the forces imposed upon them.

The interesting point here is the confirmation of laboratory investigation. It is quite evident that the "spinal shock" occurred almost exclusively in a direction aboral to the injury. Gross haemorrhage was found from the sixth cervical to the fourth thoracic segments. Cellular damage was recognized at the fourth cervical, that is 2 segments above the gross damage while similar changes were seen in all sections below the gross lesion. Physiologically the evidence is identical. The phrenic nuclei were evidently excitable within a few minutes while only the lowest reflex arcs, those responsible for the movements of the toes, were excitable after 4 weeks.

It is rather futile to speculate as to the fate of the baby if it had lived longer. The cellular changes were widely distributed but in all probability a considerable amount of reflex activity would have taken place. For lack of better terms it may be proper to regard the condition of the lower cord cells as "isolation dystrophy"<sup>2</sup>

<sup>2</sup> For permission to report this case we are indebted to the Obstetrical, Pediatric and Pathological Services of the New Haven General Hospital. The clinical examination was made by Dr. E. A. Park.

*Case 8 Transection with severe sepsis of urinary tract Autopsy* P J a colored child of one year came under the observation of the physicians at the Rochester (N Y) General Hospital and it is to Dr A D Kaiser of that city that we are indebted for the following report

*"First entry September 1, 1924, fretfulness and fever* Mother and father well One brother, age 5 weeks One miscarriage, no stillbirths Home environment good

"Full term, forceps delivery, weighing 6 pounds at birth Color and cry good Breast fed for only brief interval then put on formula of diluted cow's milk and Dextrin Maltose, has never gained as child should

"Three days ago child became constipated, very fretful, cried easily Enema used with good results Because of fever child was admitted

"Physical examination showed a colored infant lying in crib, apparently quite sick, feverish and irritable Fairly well nourished Cranio-tables Marked Harrison's groove, rachitic rosary, abdomen lax and prominent, generalized tenderness over all of abdomen Extremities—child does not seem to move legs well Poorly sustained double ankle clonus Urine examination showed trace of albumen, moderate pus cells, and many motile bacilli A diagnosis of pyelitis was made on basis of fever and urinalysis Child was put on potassium citrate solution q s to give alkaline urine Fever dropped from 104 to 99 degrees in 4 days, remaining there till eleventh day when it rose to 101° Daily urine examinations showed traces of albumen in all specimens and many white blood cells Child was discharged on the fourteenth day to Out-Patient Department for follow-up of condition Despite the fever the child did not seem acutely ill and took feedings well while on the Ward

*"Second entry to hospital September 17, 1924* Child was brought in today for an acute diarrhea of 3 days and refusal to take food Examination was about as it was on first entry except the child did not look so acutely ill Given a colonic irrigation and put on a fat-free formula which gave relief of all symptoms There was no perceptible fever Urinalysis the same as before

"It was noticed that the child was not able to stand or sit up and that the lower extremities seemed to take the position placed in with no attempt to move same Because of neurological symptoms the Neurologist was called who noted the following positive findings

"Baby presents a flaccid paraplegia but with double ankle clonus and Babinski, knee jerks present but not exaggerated Cutaneous sensibility preserved over lower limbs apparently, but muscles are soft and flabby and without tone Advise spinal fluid studies'

"Spinal puncture was done on three separate occasions by three different operators, in all cases it was a "dry tap " For two weeks the child seemed to hold its own, took feedings well and was apparently happy despite a fever which persisted, at times going above 102°, and at times to normal. The child was gone over thoroughly for possible causes of fever other than a urinary infection but none found except a transitory flare-up following a successful "take" for small pox vaccination. The child's bladder was noted to be distended and with abdominal pressure residual urine could be easily forced out. It was thought that the fever developed from the absorption of a residual infected urine. Catheter specimen of urine showed *Bacillus coli* (profuse growth). Widal negative. Blood culture negative. X-ray of chest showed nothing definite in the way of pathology. Orthopedic Service asked to see case. X-ray of body of 5th lumbar spine was suggestive of tubercular process on account of its moth-eaten appearance. Tuberculin tests were negative. White blood counts ranged from 9,000 to 13,000 while on Ward. Vaginal smear negative for gonococci. Nose and throat cultures repeatedly negative for K L bacilli. Blood Wassermann negative.

"Lumbar punctures were again attempted in different spaces, it seemed as if the needle were felt to enter dura with a sense of less resistance but spinal fluid was never obtained. To rule out possible cord tumor a cisterna tap was done under anaesthesia but not with best results as fluid was bloody making cytological tests worthless. Fluid was under no increased tension however and child suffered no after effects.

"Dr E A Park of New Haven saw the infant and suggested birth cord injury. Parents were asked to notify attending obstetrician who said that case was one of a difficult labor with anesthesia. A *version* was done and force needed at time was sufficient to fracture one of baby's femurs.

"Summing the case up it appears that the diagnosis rests with a cord injury at a point high enough to interfere with abdominal musculature and sphincteric control.

"Last note on child is that the fever remains, there is still a residue of urine yet child has even gained in weight to a slight extent. Its progress will be noted in the Out-Patient Department.

"After discharge from the hospital in November 1924, the child became worse and returned in a week.

"The child died during January, 1925 "

*Autopsy* showed a crush in the cord with considerable infiltration of tissue at dorsal region. The other organs were essentially normal except for an infected bladder.

The diagnosis of cord lesion was very evident at post mortem examination. Child was 2½ years old at death.

*Comment* In view of the outcome of this case it is worth going back over the history. In the first place the delivery was misstated by the informants at the start. This agrees with our experience in many cases. Any birth without instruments is often regarded as normal, any anesthesia implies instruments to the layman, moreover it is, of course, a very ordinary thing to do a version after attempting forceps. In this case the difficulty of the delivery was evidenced by the incidental fracture of a femur.

Further it is worth noting that in spite of the cord injury no difficulty was experienced in initiating respiration.

The possibility that reflex activity was confused with consciousness of pain or touch is suggested, especially in view of the neurological consultant's use of "apparently" in noting the presence of sensation over the legs.

The repeated failures to obtain spinal fluid are again in accord with our findings. We surmise that the arachnoid may have reacted to the trauma by widespread adhesions thus obliterating the subarachnoid space.

The brief autopsy report is, of course, conclusive and rereading of the clinical notes is instructive.

*Case 9 Transection No reflex activity Dislocation of vertebral column Operation* In October, 1924, D. R. was brought to the Out-Patient Department of the Children's Hospital at the age of 5 weeks, with the following history:

The mother, a primipara, had been allowed to remain in labor for 50 hours, with 24 hours of hard pains, before it was appreciated that the child lay in a transverse position. Podalic version and extraction were then performed with difficulty. The baby weighed 8½ pounds and apparently required no resuscitation. At the end of 2 weeks mother and child went home from the hospital. Then for the first time the parents noticed that the baby's legs were completely paralyzed, although in other respects he seemed normal.

When examined at 5 weeks of age he presented a very typical picture of diffuse cord injury extending from the cervical region to the sacral. The arms were held adducted at the shoulders in moderate external rotation and

supination, strongly flexed at the elbows with fingers flexed over adducted thumbs. Departure from this habitual position was very slight, although no one group of muscles appeared completely paralyzed. The trunk was totally paralyzed. Breathing was wholly abdominal. The lower ribs were retracted and the abdomen flabby with bulging flanks. The legs were flaccid and showed neither voluntary nor reflex activity. The sphincters likewise, were patulous and sensation was wholly lacking below the nipples. Roentgenograms at this time showed a dislocation of the twelfth thoracic vertebra on the first lumbar. Although this was well below the upper level of functional disability, it was felt that an operation to relieve pressure at this point offered the best hope of improvement. Accordingly laminectomy of the eleventh and twelfth thoracic and the first lumbar vertebrae was performed. Thereafter, the patient received treatment in the muscle-training clinic.

The child at 11 months old was well nourished and mentally alert. The arms had steadily improved in function and were strong and well used. By means of the arms alone he could drag his flaccid body across the floor. The lower trunk was still so weak that he could not maintain a sitting position without support. Placed in a prone position, he was able to raise the upper trunk on his arms and to twist the body to the left until he almost assumed a sitting position, still supported by his arms. In this twisted position the lower back showed an extreme lordosis and scoliosis. The true scoliosis, however, was very slight. The chest was asymmetrical, the right side being much flatter than the left. The lower ribs on both sides retracted with inspiration. The abdomen was exceedingly flabby and showed no reflexes. Urine dribbled from the bladder in small amounts every few minutes. It was clear. The legs were flaccid and showed no activity either voluntary or reflex. Sensation had partially returned over the upper abdomen but was wholly absent in the legs (figs 19 and 20).

In March, 1926, at 18 months, the child developed widespread ulcers over the genitals and the sacrum, in spite of extraordinarily good care. The complete anesthesia and paralysis persisted.

*Comment* In this case the obstetrical error lay in delay of recognition of an abnormal position. The actual delivery, in spite of its unfortunate consequences, was presumably done with skill as the situation at the time of operation, was desperate with an  $8\frac{1}{2}$  pound baby in a primipara. To the best of our knowledge the occurrence of dorsal or lumbar dislocation as a result of obstetrical force is not recorded in the literature, except by Holman in 1919 and by Ford in

1925 The possibility of relief by operation was of course very remote, but in view of our entire ignorance of the pathological condition we felt justified in urging it. The incision was not carried through the dura, the surgeon, quite properly, feeling that in the absence of tension no good could be done to balance the risk of sepsis. By a frame complete correction was maintained but no recovery of function occurred.

The evidence of physiological transection is conclusive. In spite

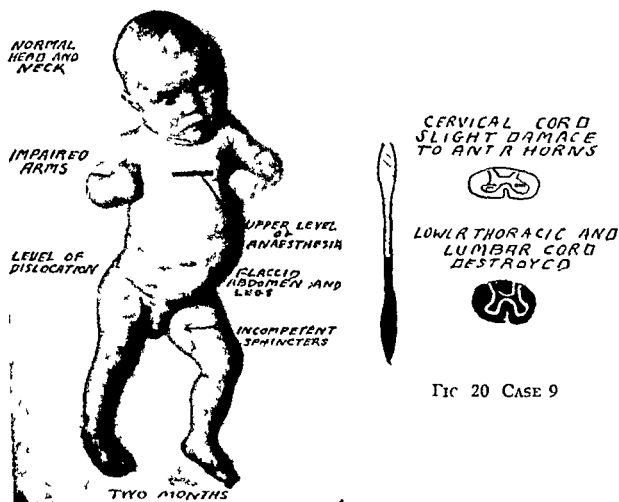


FIG 20 CASE 9

FIG 19 CASE 9

of this no urinary sepsis or trophic ulcers occurred for nearly 18 months. The meticulous care given by the mother was probably responsible for the late occurrence of ulcers.

*Case 10 Flaccid paraplegia with anesthesia and loss of sphincter control, no ulcers, no reflex activity. Sacral above injury.* R. H. W., a full term male infant, was born by breech extraction December 28, 1921. The attending physician, an experienced operator in a leading clinic in a city of

considerable size, reports as follows "The maternal pelvic measurements were normal The mother was a 31 year old primipara After twelve hours of labor the os was fully dilated but the breech was only partly engaged Under anaesthesia both feet were brought down and traction, in a straight line, employed No unusual force was employed As the pelvis was delivered a snap was heard No definite explanation suggested itself and after pause steady traction was resumed with suprapubic pressure by a nurse A second snap was heard but delivery was effected some 6 or 7 minutes after the efforts at extraction began Resuscitation was difficult, the baby had a broken clavicle and did not move its legs "

The history subsequent to delivery and prior to the examination by one of us in April 1924 when the baby was 16 months old is as follows

No return of power to the legs occurred The sphincters remained without tone On the other hand, the child used its arms well and could crawl about but dragged the flaccid legs after him He could sit by supporting his trunk with his arms Mentally he was a bright responsive child The spine showed lateral and antero-posterior deformities below the costal margin Several attacks of urinary infection were observed

Physical examination at the time the child was seen by us revealed no new information of importance The baby was bright with strong arms and shoulders The lower trunk and both legs were entirely flaccid The child dragged itself about with its flail-like lower half following like the legs of a swimmer using arms alone The shoulders, arms and upper chest were covered with beads of sweat after slight exertion A very definite line separated this wet area from the dry lower trunk and legs The skin of the head and neck though moist, was not wet The lower chest flared and distinct indrawing with inspiration was seen The upper chest moved symmetrically There was no rosary or other suggestion of rickets The spine showed easily correctible deformities when the child was supported in a sitting position Both sphincters were flaccid and abdominal pressure caused evacuation of the bowels and bladder The urine was cloudy with pus and bacilli on microscopic examination Lumbar puncture showed normal fluid without evidence of obstruction on jugular pressure The sensory disturbances are noted on the chart (fig 21)

*Comment* The chain of evidence here is complete even to the audible snaps appreciated by the obstetrician Apparently one of the 2 sounds heard was the giving way of the clavicle and it is reasonable to suppose the other was associated with injury to the spinal column or the dura surrounding the cord The fact that x-ray study did not

revel fracture of the spine is to be expected as the break if present occurs in most cases in the intervertebral discs or along epiphyseal lines rather than in the very small amount of calcified bone

The exact anatomical status is relatively unimportant. Conceivably destruction of the cord below the upper level of involvement occurred at birth. An equally valid assumption is that owing to early and severe bladder infection the isolated cord never recovered sufficiently to direct reflex activity. This explanation of course is consistent with

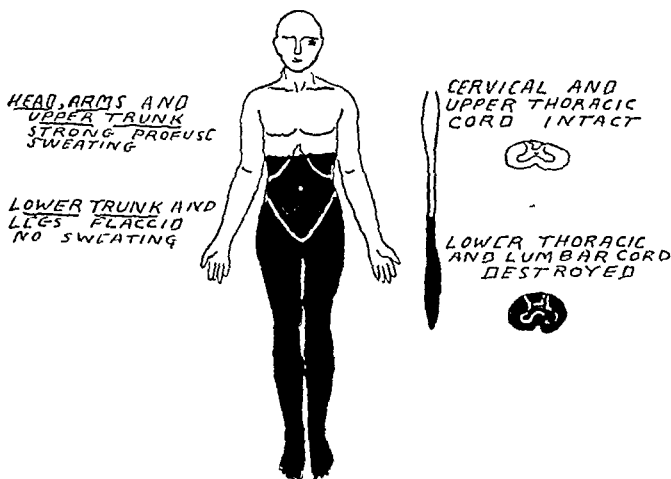


FIG. 21 CASE 10

observations made by several writers that in the presence of infection reflex activity may become less active or even be abolished. In any case, from a physiological standpoint, there is no evidence of activity below a level in the vicinity of the sixth thoracic segment.

**Case 11 Severe cord injury. Brachial palsy. Head delivery.** A A was brought to the Out-Patient Department in 1923 at 2 months of age. The obstetrical history was striking. A midwife conducted the labor. The head emerged but the shoulders did not follow. Traction on the head was unsuccessful. Strong traction with fingers in the axilla was likewise



futile She then gave up and went for medical assistance but the child was born before she returned

The baby was resuscitated without difficulty but the right arm and both legs were completely paralyzed At 2 weeks some motion returned to the fingers and at 3 weeks motion of the legs was noted

At first glance the child at 2 months showed evidence of severe "upper arm" palsy on the right and one of us sent her to the Muscle Training Clinic with that diagnosis A more careful history and an adequate examination revealed the true situation

The right arm was extended, adducted and internally rotated with practically no power except in the triceps, the pronators and the flexors of wrist and fingers The left arm was stiff, held close to the body, with flexion at elbow, wrist and fingers All reflexes on the left were increased The whole

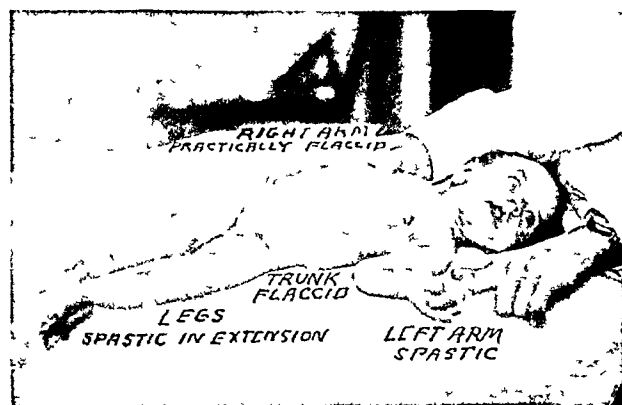


FIG 22 CASE 11

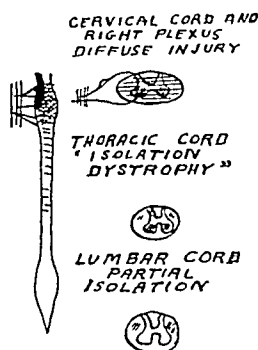


FIG 23 CASE 11

trunk was practically motionless with pure diaphragmatic breathing The legs moved feebly and were habitually flexed at hips and knees with extension of the ankles The reflexes, however, were very much increased with clonus at the knees and ankles and bilateral Babinski sign The bladder was emptied at regular intervals with a good stream Sensation could not be tested accurately, but no clear anesthesia was found No evidence of rickets or of vertebral injury or anomaly was seen in roentgenograms

During the next month the arm improved a little, the legs were habitually extended instead of flexed as at first The photograph was taken at this time (figs 22 and 23)

*Comment* The traction upon the head and arms against the still engaged trunk was evidently excessive. Moreover, it was clearly not necessary. The child breathed soon after delivery in spite of evident cord injury. The right arm showed the usual picture of injury of the upper roots. The cord involvement was obviously not total transection, but enough anterior horn cells were damaged to cause general and persistent weakness of the trunk. The spasticity of the legs was presumably due to partial interruption of motor tracts. Enough sensory fibers escaped to allow sensory impulses to reach the brain. In view of the impossibility of testing fine variations it is possible that all tracts were somewhat involved. We believe that this child suffered from a true avulsion of the brachial plexus with diffuse cord injury. There is no reason to suspect cerebral damage. One point which is worth mentioning is that no evidence of sympathetic involvement was observed. Cobb showed, by study of war wounds, that the sympathetic fibers often escape when the injury is in the cord rather than the lower roots of the plexus. Various other cases in this series reinforce his conclusions.

*Case 12 Flaccid paraplegia. Reflex sphincters. Trophic ulcers.* K. A. was brought to the Out-Patient Department of the Children's Hospital at the age of 5 months because of complete paralysis of the legs since birth. She was the second child and weighed 7½ pounds at birth. A breech extraction had been accomplished with considerable difficulty. Two people had been required to hold the mother while the doctor pulled with great force. A flaccid paralysis of the legs was immediately noticed, which had persisted, together with a complete lack of sphincter control.

On physical examination at 5 months the baby appeared bright and vigorous with normal head, arms and chest. The spine was straight. The abdomen was very soft and exhibited no reflexes, but was not wholly toneless. The legs were absolutely flail like showing neither voluntary nor reflex activity. Urine dribbled from the bladder and could readily be expressed by slight abdominal pressure. Sensation was totally absent below the chest and normal above. Lumbar puncture, attempted 3 times by a competent operator, resulted in dry taps. A roentgenogram of the spine was negative (figs. 24 and 25).

This child has been treated in the muscle training clinic for a year and a half and has enjoyed excellent health and shown normal development.



FIG 24 CASE 12

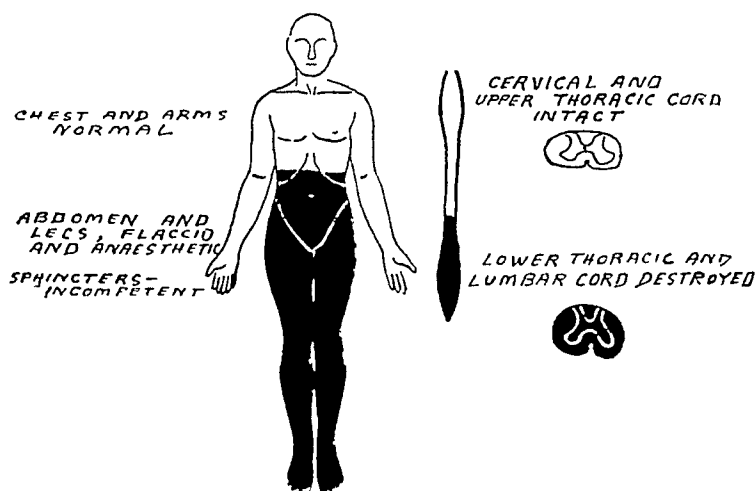


FIG 25 CASE 12

She is now  $2\frac{1}{2}$  years old. She began to talk at a year, crept at 13 months, dragging herself over the floor by the arms, and sat up alone at 16 months. The bladder and rectum became automatic at one year. Urine is now passed at hourly intervals, stools 2 or 3 times a day. The abdominal muscles have steadily increased in strength, the abdominal reflexes returning one by one so that at present only the right lower is unobtainable. Flexion appeared in the hips at 9 to 10 months and has increased slightly. There are no voluntary movements below the hips and not a sign of reflex activity. The back is well supported with straight spine. Sensation has partially returned over the abdomen but is still almost completely absent below the hips. A deep trophic ulcer which developed recently over the coccyx gave no discomfort whatsoever.

*Comment.* The injury in this case obviously had its upper limit in the mid thoracic region but must have extended downward to include most of the lumbar cord, since no reflex activity has developed in the legs in the course of 2 years. During this time the upper level of weakness and anesthesia has steadily receded, and there is every reason to hope that with the aid of apparatus this child will be able to walk. For this reason it is necessary to make every effort to control the progress of the bedsore.

*Case 13. Complete transection with elaborate reflex activity.* A. B. was admitted to the Children's Hospital in February, 1925, when nearly 2 years old.

The mother, a primipara, had been delivered with great difficulty because the child was large, weighing 9 pounds, and the presentation was a breech. Extreme traction had been exerted upon the child's legs and an attempt to bring down the right arm had resulted in a fracture of the humerus. At birth the child was found to have a complete flaccid paralysis of the legs. After several days the muscles of the legs are said to have regained some power but never to have moved normally. As time went on, it became evident that the trunk, also, was very weak. The arms were uninvolved except for the fractured right humerus. The child's mental development had been entirely satisfactory and he talked at one year.

Physical examination showed a healthy child of nearly 2 years, mentally alert and physically normal above the nipple line. The arms were strong and well used. Sitting up, however, was impossible because of almost complete paralysis from the nipples down. The lower half of the chest showed intercostal weakness, more marked on the right than on the left.

The most obvious movement was retraction on inspiration. The abdomen was completely atonic with bulging flanks and absent reflexes. The bladder and rectum were essentially automatic, although there was some dribbling of urine at times. The trunk was very weak and when the child was

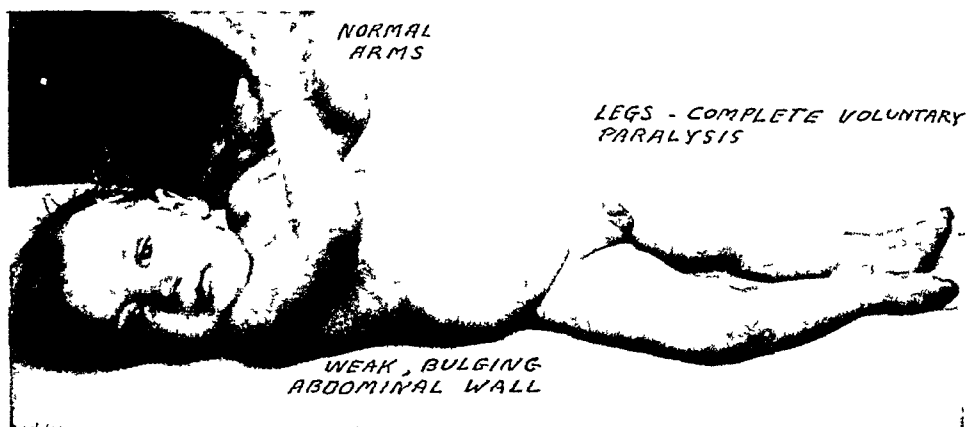


FIG 26 CASE 13

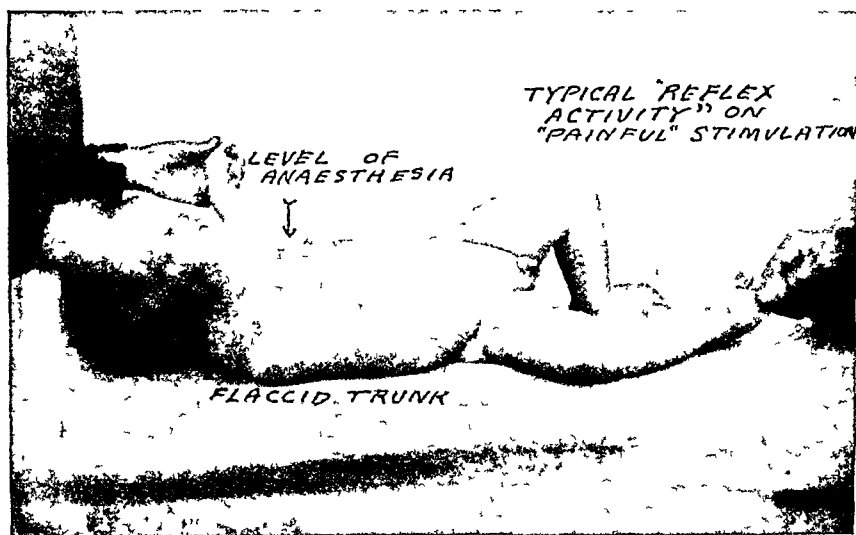


FIG 27 CASE 13

placed in a sitting position, the trunk fell forward so that the chest rested on the legs. The spine showed a scoliosis with right thoracic curvature. The legs had very little tone and lay externally rotated with slightly flexed knees and hips and extended feet, with shortened Achilles tendons. No voluntary movements of the legs could be detected but their reflex activity

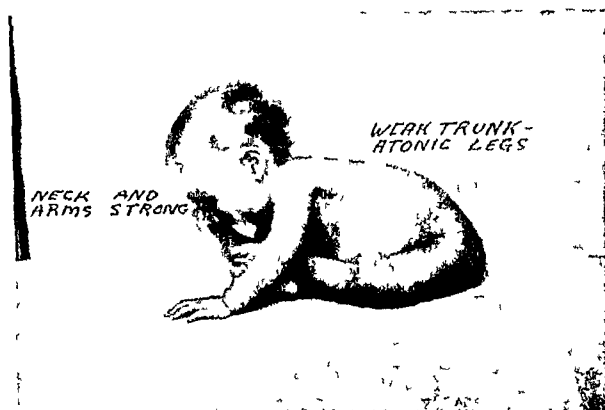


FIG 28 CASE 13

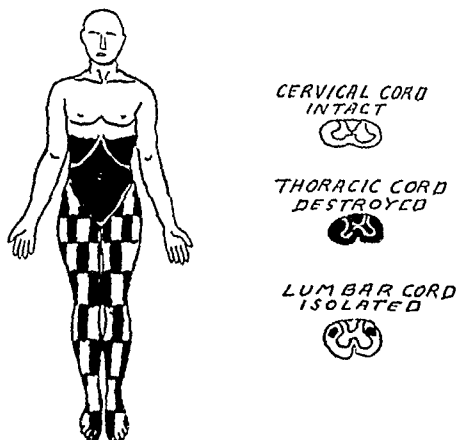


FIG 29 CASE 13

was pronounced. The knee jerks and ankle jerks were present on both sides and normal in extent. There was bilateral ankle clonus and Babinski sign. Upon painful stimulation of either leg a characteristic mass reflex was exhibited with marked flexion of both legs. At times it was possible to elicit a crossed extension reflex. Sensation was normal above the nipple line but entirely absent below (figs 26, 27, 28 and 29)



FIG 30 CASE 14 WITHOUT STIMULATION



FIG 31 CASE 14 AFTER PINCHING

*Comment* As a result of an extremely difficult breech birth this patient had obviously suffered a severe injury amounting to complete transection of the upper thoracic cord. Below this level the flaccid chest and abdomen indicated extensive anterior horn cell destruction in the corresponding thoracic segments, whereas the lumbar and

sacral portions of the cord must have remained essentially intact to permit of such striking reflex activity in the legs

Naturally a case of this sort presents a serious therapeutic problem. The fact that the evidence suggests that the lumbar enlargement is intact makes it probable that apparatus can be fitted without danger of ulcers. It is therefore obligatory to prevent important deformities if possible. On the whole, it makes little difference whether or not the Achilles tendons become tight, for a simple and painless correction will be possible. It is, however, of very considerable importance to

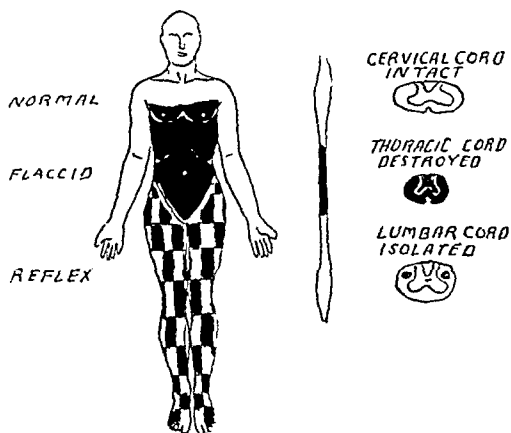


FIG 32 CHART OF CASE 14

prevent serious scoliosis. The child is therefore kept on a Bradford frame much of the time. Later by a properly devised corset and long splints it is probable that walking with crutches will be obtained. In any case, we do not feel that, in spite of the present evidence of transection, we know enough of the possibility of improvement to deny that voluntary activity of some value may occur. The child is intelligent with full use of his arms. Bladder and rectum are automatic, so that infection of the urinary tract is by no means inevitable and life is not directly threatened. With these assets we feel justified in planning for unexpected improvement.



*Case 14 Complete transection Reflex activity Death from urinary sepsis* Baby G was admitted to the Infant's Hospital on October 30, 1924, at 3 weeks of age The breech delivery in a multipara had not been difficult

The situation at entrance was clear There was anesthesia below the third rib, a flaccid trunk and reflex legs (figs 30, 31 and 32) The child died at 6 weeks from urinary sepsis No autopsy was allowed

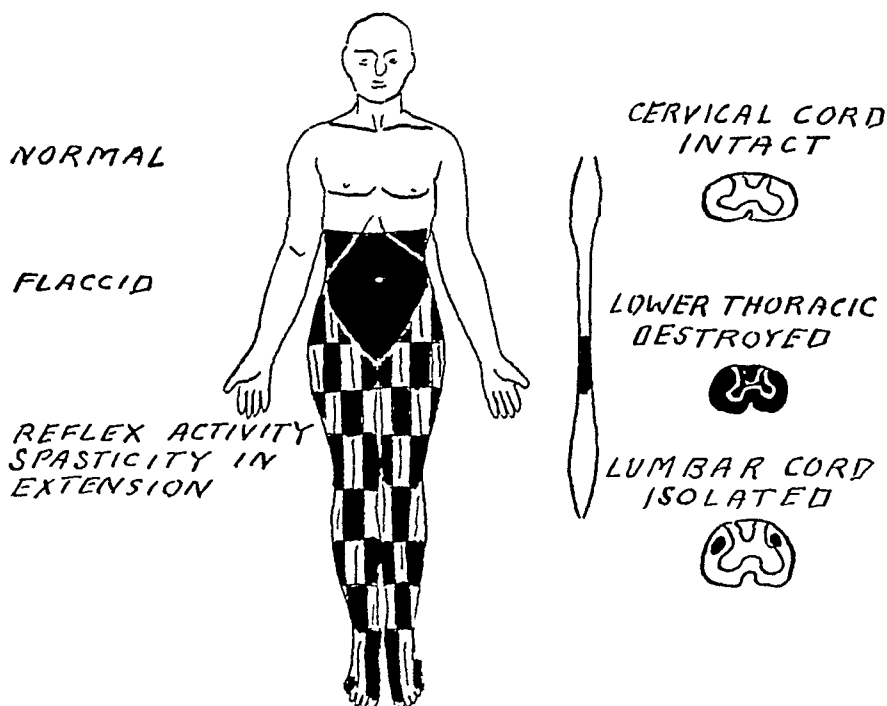


FIG 33 CHART OF CASE 15

*Comment* The apparently easy extraction was performed in one of the best obstetrical hospitals in the country The vertebral column was apparently not injured The motor phenomena in the legs are identical with those described by Parrot in the first adequately reported case in 1870

*Case 15 Transection with reflex activity after head delivery* L W was admitted to the Children's Hospital in 1923 at the age of 3 years She was the second child

The mother stated that after prolonged labor, instruments had been applied to the child's head and delivery effected with difficulty From birth

the baby had shown a complete voluntary paralysis of the legs and incontinence of urine and feces. The only leg movements appeared to have been of a reflex type.

Examination showed that her head, arms and chest were normal. Below the costal margin, however, the trunk was flaccid. Abdominal reflexes were absent. The child sat with a rounded lumbar kyphosis and moderate right dorso-lumbar scoliosis. There were no voluntary movements in the legs but extremely active reflexes. Exaggerated knee jerks and Babinski's sign was present on both sides. Ankle clonus was sustained longer on the right than on the left. Sensation was wholly absent below the costal margin. The bladder and rectum were automatic (fig. 33).

A roentgenogram of the spine showed no departure from the normal. On lumbar puncture a free flow of fluid was obtained with no evidence of block.

*Comment.* The birth history in this instance departs from the usual story of difficult breech extraction. But the delivery, though vertex, had been accomplished with great difficulty, and in view of the history of paralysis from birth it is altogether probable that an injury to the cord was sustained at that time. The upper level of the lesion was evidently in the lower thoracic region. Flaccidity and absent reflexes of the abdomen again indicate anterior horn cell damage over several segments, whereas the reflex arc was not demonstrably impaired in the lumbar and sacral regions.

*Case 16. Severe injury with reflex activity of one leg.* O. L. 2 months old was seen February 6, 1926, in consultation at the New England Hospital for Women and Children. The boy was born under peculiar circumstances. The mother, an unmarried feeble-minded girl, appeared at another hospital with ruptured membranes and a presenting foot, denying labor, or even pregnancy. Very naturally a rapid extraction was done without much expectation of procuring a living baby. The least possible intravaginal manipulation was undertaken.

The child on examination seemed bright enough. No evidence of cranial injury existed. The baby lay in a distorted opisthotonos due partly to spasm and partly to weakness. The breathing was almost entirely diaphragmatic. The abdomen bulged. The sphincters were probably automatic though the anus was decidedly protruded. The bladder was empty.

The right leg was flexed at the hip with strong contractures, chiefly of the femoral fascia. The left leg was entirely flaccid. No voluntary motion

was observed on either side, but distinct reflex movements of the toes and ankle on the right could be elicited. No reflexes could be obtained on the left.

Sensation was absent from the fifth rib down and diminished to the second rib. The arms were normal (fig. 34).

*Comment* The bizarre situation when the mother applied for treatment justified any procedure which could deliver the child without too much danger of infection of the mother.

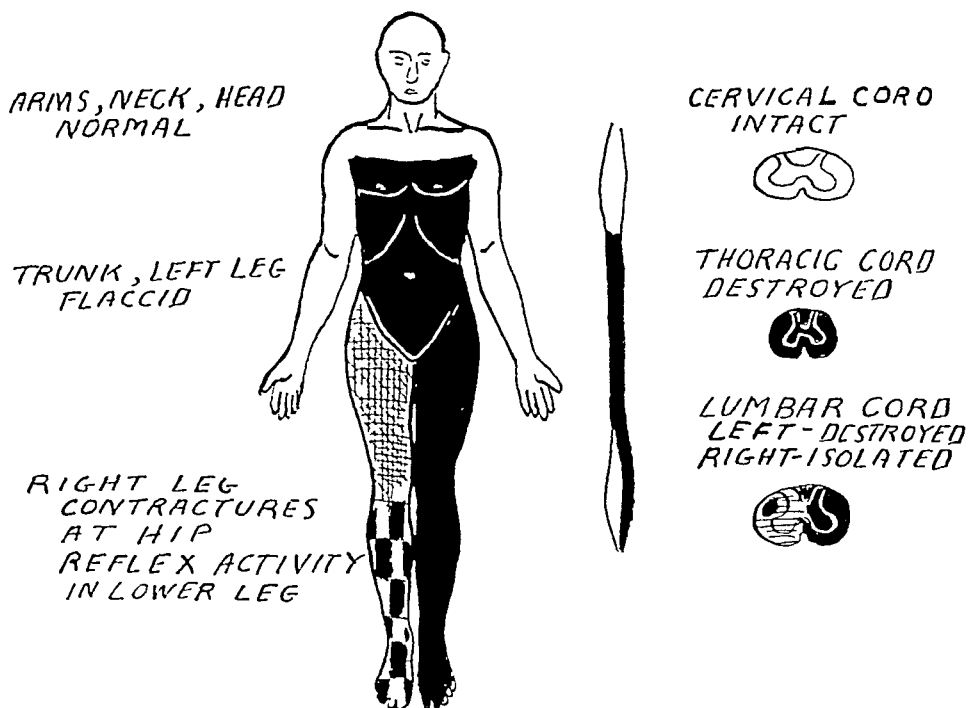


FIG 34 CHART OF CASE 16

Under the circumstances it is not surprising that the baby suffered. It was obvious that almost the whole of the thoracic cord was impaired, though the persistent opisthotonos showed that the erector spinae group of muscles were not completely without nerve supply. The contractures about the right hip and the reflex activity of the right leg and foot, with the automatic bladder suggested that the right side of the lumbar enlargement, at least, was more or less intact.

The child suddenly died and owing to strong religious feelings on

the mother's part autopsy was absolutely refused. In going over the literature a picture of a child with essentially the same distortions was found in an article by Laffont to which reference is made later. In that case the dura was torn across with cord injury high in the thoracic region.

*Case 17 Diffuse injury with scoliosis as most conspicuous sign* M B a Polish girl of 6 years and 4 months was first admitted to the Orthopedic Out-Patient Department in July, 1922.

Two of the mother's babies were born dead, one other child is well. The order of pregnancies is not stated in the record. The mother stated that she had been instrumentally delivered, with great difficulty. She knew no details and a request for information from the attending physician was not answered.

After birth the child was motionless and limp for 3 days, then "stiff" all over. This stiffness persisted. As far as the history, obtained through interpreters, went there was nothing to suggest any mental defect. Speech, control of sphincters, etc., were not remarkable.

The posture of the child with increasing spinal curvature and the stiff awkward gait were the disabilities which led to the first admission. A diagnosis of "cerebral spastic" with scoliosis was made by orthopedists and repeated jackets applied. On account of tightness of the Achilles tendons she was admitted for study and treatment to the wards on October 30, 1923 at 7 years and 8 months.

The condition at that time was essentially as follows. The scoliosis was still very obvious in spite of the careful treatment the child had received for a year or more. The gait was stiff and awkward. She was handicapped by the asymmetry of the trunk as well as by the stiffness of her legs. The trunk in addition to the deformity seen in the photographs and described in the x-ray reports showed relative immobility of the right chest, and firmness of the abdominal wall (figs 35, 36, 37 and 38).

In general, the signs of special neurological interest were,

- 1 Definite narrowing of the palpebral fissure on the left
- 2 Weakness of left arm with definite restriction of external rotation at the shoulder and supination at the wrist. The deep reflexes of both arms were rather lively.
- 3 Trunk weakness especially of the right chest and the upper abdomen. The abdominal reflexes were obtained only below the umbilicus.
- 4 Spasticity in extension of both legs with slight adductor tightness and

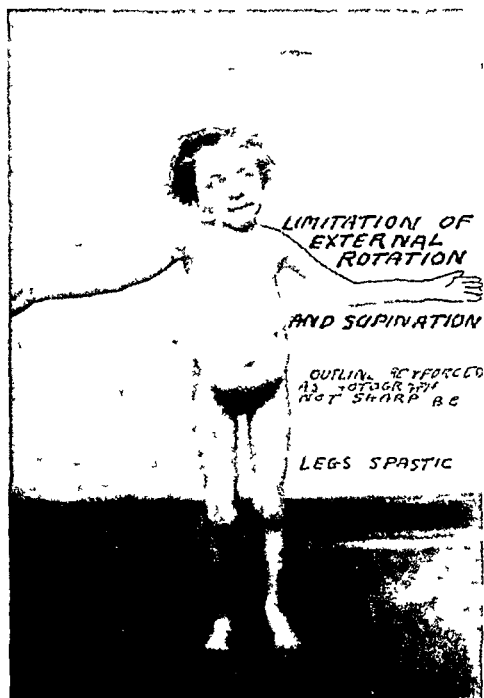


FIG 35 CASE 17



FIG 36 CASE 17



FIG 37 CASE 17

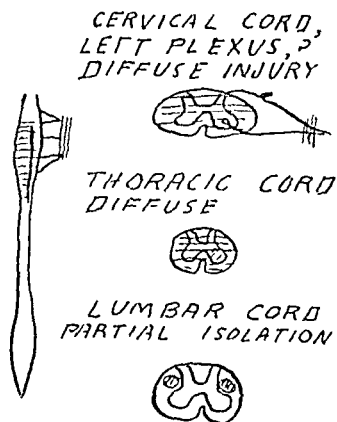


FIG 38 CASE 17

marked equinus, especially on the left. Bilateral increase of reflexes was noted with ankle clonus and positive Babinski sign on both sides.

5. No sensory disturbances or vasomotor changes were made out.

The x-ray report was as follows: "Films of the entire spine show a very marked scoliosis to the right in the mid-dorsal region, there is definite

flattening of the vertebrae on the left. There is also a definite kyphosis in the mid-dorsal region. The process appears to be postural rather than destructive."

As an orthopedic problem the case presents various difficulties which we are not prepared to discuss. The neurological phenomena suggest a diffuse cord lesion high enough to involve some of the sympathetic fibers on the left and low enough to involve the anterior horn cells of the thoracic segments and to a slight extent both pyramidal tracts. The child spoke little English and no competent interpreter was available in the wards. Fine sensory changes, therefore, were probably not discernible. However, she cooperated well and it was evident that no gross disturbances existed.

Re-questioning of the parents probably involved a strong suggestion, but brought out a statement that the doctor turned the baby after attempting to apply forceps. This information was of dubious accuracy, but renewed attempts to reach the doctor failed.

The most interesting argument was that concerning the question of whether or not a congenital scoliosis was responsible for the spasticity. Lumbar puncture was not allowed. However, no evidence of congenital anomaly was found on x-ray examination.

The type of disability is quite comparable with that seen in case 5. The difficulty, though not the exact nature of the delivery, is known, and the probable diagnosis of cord injury was agreed to by numerous orthopedic and neurological consultants.

The obvious therapeutic problems are, of course, purely orthopedic.

*Case 18. Diffuse cord injury following apparently normal labor.* C. C. was first seen at the hospital in January, 1924, when 8 years old. The birth history was not in any way remarkable. It is reported as an easy cephalic delivery. However, he had in infancy a weak abdominal wall with protrusion at the umbilicus and both groins. One of these ruptures was so large that operation was performed at 11 months. The boy developed normally except that he did not attempt to walk until he was 5 years old. Since then he has walked with a stiff awkward shuffle.

When we first saw him he was entirely normal except for the legs. The arms were in no way abnormal. The abdominal wall was strong. Mentally he was unusually bright, talking both French and English without hesitation. The legs were spastic with contractures of the flexors and

adductors at the hips, and of the hamstrings at the knee. All the tendon reflexes were hyperactive. No sensory difficulties were made out (fig 39).

Normal fluid and normal pressure relations were revealed by lumbar puncture. The Wassermann was negative. Roentgenograms were negative.

The evidence of injury is lacking. However, none of the ordinary causes of cord damage were discovered. The early evidence of transient weakness of the abdominal wall, with permanent spasticity of the legs, justifies the assumption that a diffuse cord injury of non-pro-

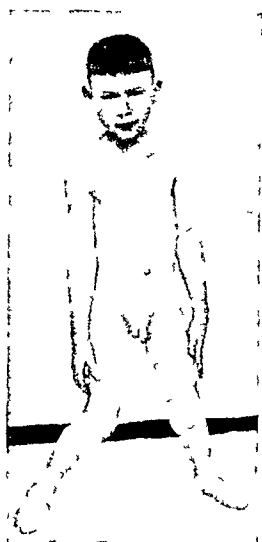


FIG 39 CASE 18 BEFORE MUSCLE TRAINING. AFTER ALCOHOL INJECTION OF OBTURATOR NERVES

gressive type exists. His condition at present is almost identical with that of case 19, where a strong presumption of cord injury is established.

The only other possibility that occurs to us is a sharply circumscribed lesion involving both leg areas of the motor cortex. Such cases occur as a result of gunshot injury, and occasionally from tumors of the falx. On the whole, such lesions in children must be very rare as the falx lies between the two leg areas. Furthermore, the cerebral lesion would not explain his temporary abdominal weakness.

Of course a postnatal injury or infection might explain the picture. There is, however, no history to point to either possibility. When

the literature is considered cases of intravertebral birth haemorrhage without obvious trauma are found

In any case the subsequent treatment of this case is interesting and relevant

It was clear to all of us at the hospital that this boy represented a group of spastic paraplegias worthy of careful therapeutic study. He was absolutely normal mentally and almost completely crippled as far as his legs were concerned. He was unable to use his legs effec-

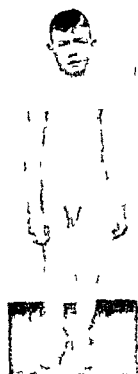


FIG 40

FIG 40 CASE 18 AFTER SYMPATHETIC RAMISECTION ON RIGHT

The symmetrical improvement is attributed by us to prolonged muscle training rather than to operation

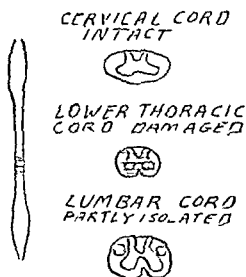


FIG 41

FIG 41 CHART OF CASE 18

tively for 2 reasons, first, on account of gross contractures, second, on account of spasticity. A long enough time had elapsed to rule out hope of spontaneous improvement.

Alcohol injection of the obturator nerves relieved the adductor spasm for a time. With muscle training and stretching of the hamstrings he did well for a period. Nine months later Dr J Hunter and Dr N D Royle saw the boy and Dr Royle did a ramisection on one side, severing the sympathetic innervation of the right leg. This did not change the situation at all.



More radical surgical interference was considered, but a prolonged physiotherapeutic regime is gradually improving the boy (figs 40 and 41) On the whole the difference between the status shown in the two photographs is due in our opinion to patient and resourceful muscle training rather than to surgical interference It may well be that more drastic surgical attack, including tenotomies would have been wise, but we believe that it is better to proceed cautiously in a young child, reserving mutilating operations until more conservative measures have definitely failed A few years of delay are not vitally important in view of steady though slow improvement

*Case 19 Slight injury of premature foetus Moderate spasticity* G W, age 4 years and 9 months, was seen in consultation by one of us in January, 1923

He was the first child During the sixth month of pregnancy the mother had a fall and started in labor with some bleeding The cervix was forcibly dilated and the attending physician delivered a small foetus by version The birth weight was said to have been about 2 pounds To the surprise of everyone the child, under a rigid premature regime, survived After a very carefully regulated early infancy disturbed by frequent respiratory infections he sat up at one year and walked with support at  $2\frac{1}{2}$  years He was unusually bright and talked well, beginning about one year

From the time of his first steps he had walked with obvious difficulty Sphincter control had been adequate for the past 2 years

Physical examination showed a child quite normal above the nipple line Nothing in the control of speech or in control of the arms suggested cerebral injury The lower chest flared out and there was obvious retraction on inspiration The spine showed a marked lordosis The abdominal wall was weak and bulged slightly The legs were spastic with patellar and ankle clonus and positive Babinski sign on both sides There was moderate contraction of the Achilles tendons The sensory examination, which was satisfactory, revealed no abnormality The mental examination by the Stanford-Binet tests showed an intelligence level of 5 years (fig 42)

*Comment* The delivery by version of a presumably non-viable foetus is of course a perfectly proper obstetrical procedure obviously justified by the situation which confronted the operator The child now suffers from a pure motor disability of very moderate severity He responded to training in a satisfactory way A proper corset cor-

rected the lordosis and simple manipulations overcame contractures. The chief difficulty happened to be one of personality. The child, quite inevitably, had been regarded as a weakling to be helped. However, by constant encouragement a reasonable attitude was obtained.

The absence of sensory changes is not surprising since the ganglion cells are outside the cord and the lesion was slight enough to avoid widespread tract destruction. The weakness of the lower trunk

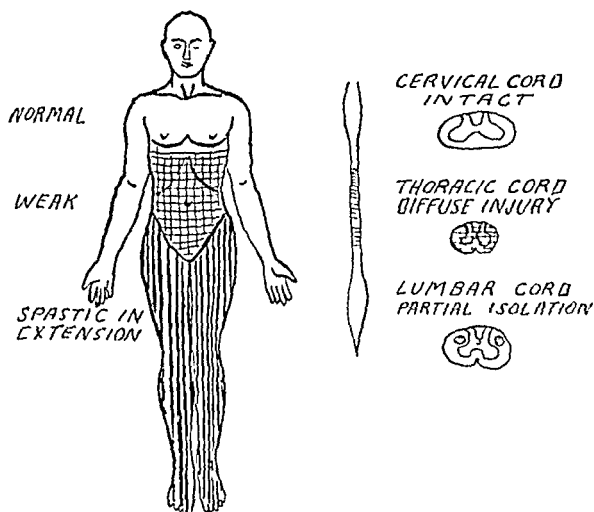


FIG 42 CHART OF CASE 19

presumably depends upon lesions in the anterior horn cells while the moderate spasticity suggests impairment but not destruction of the pyramidal tracts. The evidence, therefore, suggests that the lesion is a diffuse, markedly incomplete damage to the lower thoracic cord due to stretching of a premature foetus in the course of a justifiable obstetric procedure.

*Case 20 Cephalic delivery. Injury of brachial plexus. Cord in place.* A C. was brought to the hospital in July, 1924, at the age of 5

months The delivery, with the aid of forceps, proceeded smoothly until the shoulders reached the perineum Great difficulty was encountered in this part of the delivery Flaccid paralysis of the right arm was noticed on the second day

When we first saw the baby he was not using the right arm at all It was quite obvious that the left arm was stiff and rather incompetent The chief limitations were in elevation at the shoulder and supination of the forearm. The chest moved poorly Both legs were rather stiff with tight-

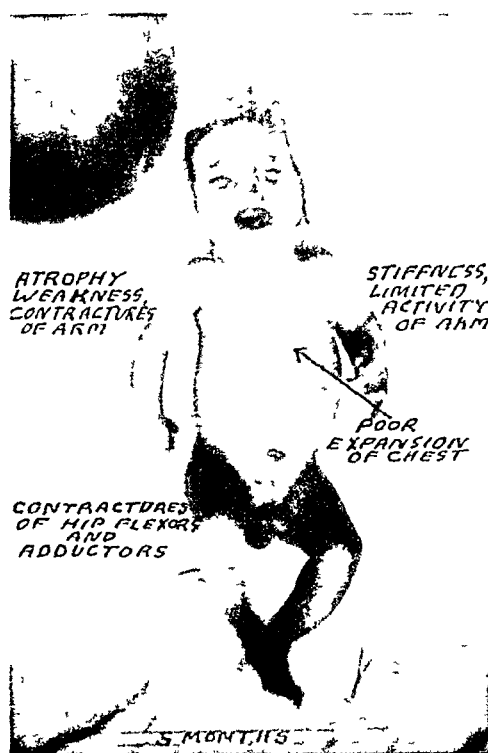


FIG 43 CASE 20

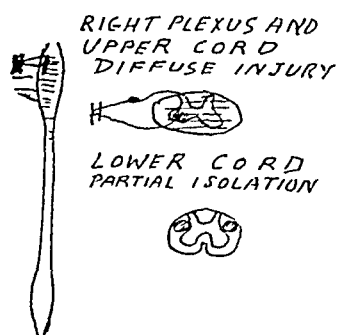


FIG 44 CASE 20

ness of the adductors and hip flexors Conventional neurological reflexes were lively but no clonus was elicited No sensory changes were made out (figs 43 and 44)

The situation was fairly clear as far as the right arm was concerned A tearing of the brachial plexus most marked in the upper roots would explain the flaccidity and the position Since no enophthalmos or inequality of the pupils was seen it was unlikely that the lower roots were seriously torn Naturally the cord might have suffered, but for evidence of cord injury the

rest of the baby needed study. The limitations of the left arm were largely due to stiffness. Theoretically, if the cord injury was at the level of the upper roots of the brachial plexus flaccidity should have been found. However, diffuse injuries, tumors and vertebral caries occasionally produce curious mixtures of weakness and stiffness. In this case elevation and supination, the motions controlled by the fifth and sixth segments, were particularly limited. The chest was not moving well. We realize, of course, the difficulty in judging the state of the intercostal musculature in babies but the limitation struck us as fairly definite. The leg spasticity and contractures were definite.

*Comment.* From a consideration of the whole situation it seemed to us that a lesion of the right brachial plexus with avulsion of the upper roots and consequent slight diffuse cord injury could explain the clinical signs. Obviously it was possible to support a different interpretation. A lesion of the plexus and a coincident cerebral injury would explain the picture. On the other hand, there was no evidence that the baby was hard to resuscitate, there was no indication that the head had not come through easily enough. There was no suggestion of mental defect or cranial nerve weakness.

After 2 months of muscle training no particular progress had been made and Dr W. E. Ladd was asked to explore the plexus. He found scar tissue with nothing much wrong with the lower roots. The upper cords were apparently represented by small bands of scar tissue running up to their disappearance into the intervertebral foramina. The scar tissue was dissected out and the wound was closed. This finding supported the clinical diagnosis to some extent. The lower roots were apparently intact. The probability that the cord suffered from traction on the plexus seemed logical.

The subsequent history is as follows. The right arm improved steadily with good motion of the fingers and wrist and some recovery of power in the upper arm. The left arm recovered completely. The legs remained stiff. The child could not sit alone though at one year he talked and was obviously bright.

We do not, of course, feel sure of anything beyond the plexus injury but the whole picture seems to be consistent with a single diffuse injury in the cervical region involving one plexus and the spinal cord due to force imposed during the delivery of the shoulders.

*Case 21 Severe subtotal cord injury with confusing signs* *Marked sweating above level of injury* R S was brought to the Children's Hospital at the age of 13 months. Although the seventh child, his mother stated that his birth had followed the longest and hardest labor she had experienced. Details of the delivery are unfortunately lacking, but we understand that forceps were tried and that the doctor at first thought that the baby was dead.

For 2 months following birth the baby scarcely moved the extremities. The legs were totally paralyzed and have remained so. The arms, held adducted over the chest, were "very weak, but after 2 months steadily improved in strength. Bladder disturbance had not been noted.

On physical examination the patient was found to be a well nourished, bright boy of 13 months, who supported his head well, grasped for objects normally, but was unable to sit up alone because of weak trunk muscles. The lower half of his body was immobile. The head showed nothing unusual. The cranial nerves functioned normally. Breathing was almost entirely abdominal, the chest expanding only slightly with deep inspiration. The chest was symmetrical and showed slight beading of the ribs and a well marked Harrison's groove with flaring costal margin. The tone of the abdominal musculature was only fair. The lower abdomen was full of hard fecal masses. The bladder was distended to a level 3 cm. below the umbilicus. No urine escaped on pressure. The arms showed no definite weakness but rather less spontaneous movement than is usual. The movements were well directed and the tendon reflexes normal. The legs were held in a position of extension at the hips, slight flexion at the knees and marked equino-varus position of the feet with plantar flexion of the toes. There were no visible voluntary movements of the legs, but very slight contractions could be felt in practically all the muscle groups. Pinching the toes of one foot caused some reflex adduction and flexion of the same leg and extension of the opposite leg, also evacuation of a little urine. Tendon reflexes, however, were absent.

The bladder had evidently become automatic, emptying itself at considerable intervals. The urinary tract was not infected. Sensation was markedly reduced from the feet to the umbilicus, moderately reduced from the umbilicus to the fourth intercostal space and normal above. Sweating, which was precipitated by excitement or excessive manipulation, such as in lumbar puncture, was profuse over the head, neck, arms and chest down to the level of the fourth interspace. Below, the skin remained absolutely dry. This sharp line delimiting the area of sweating, and also of flushing, could be demonstrated most dramatically by wiping the skin dry and then

watching the rapidly forming beads of sweat reappear in exactly the same area (figs 45 and 46)

A roentgenogram of the spine showed no deviation from the normal. Blood Wassermann and spinal fluid were negative.

*Comment* We have no details of labor here. In view of 6 previous easier labors it is fair to surmise that some gross abnormality of position resulted in dystocia.

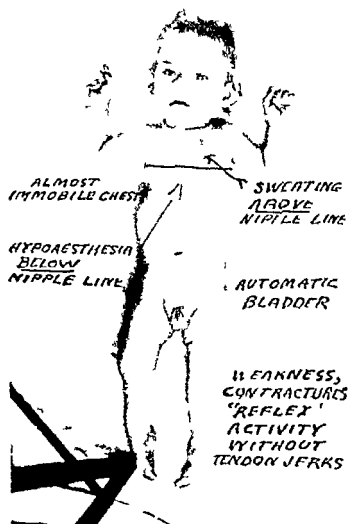


FIG 45 CASE 21

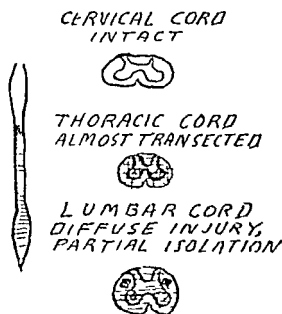


FIG 46 CASE 21

From the fourth thoracic interspace up this baby was normal. From the same level down he was almost completely paralyzed and anesthetic. It seems scarcely possible that such a picture could be produced by a lesion elsewhere than in the cord, a lesion presumably resulting from trauma at birth.

The original upper level of disability was evidently in the cervical

region involving the arms. From the complete functional recovery of the arms we may infer that there was little or no destruction of cord substance at this level, but that these segments had been temporarily incapacitated by "shock" or edema or hemorrhage of very slight extent. The upper level of permanent damage is further indicated by the sharply defined area of sweating of which the lower border corresponds to the upper border of impaired sensation and muscular weakness. The location of the sweating from the fourth interspace up places the lesion, according to Riddoch's observations, in the mid

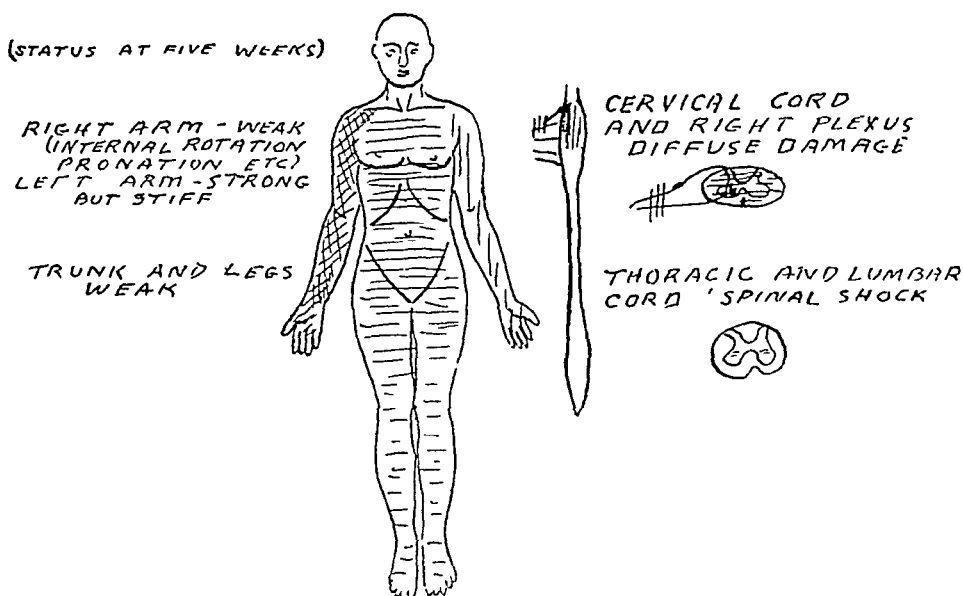


FIG 47 CHART OF CASE 22

thoracic region. From a practical standpoint the injury amounted to a practically complete transection in the thoracic region with a sufficiently intact lumbar and sacral cord to permit of reflex activity of the legs and an automatic bladder.

Hope of improvement depends, of course, on the possibility that a little voluntary power exists. It is possible that as the child grows older he can be taught to utilize the remnants of normal tissue which are left. In the few months since he came under observation no promising improvement has occurred. In fact, on the whole, his muscles are less normal on palpation. Of course, it is obvious that an

almost isolated cord has a relatively slight viability, so that any infection may be followed by lessening of activity

*Case 22 Cephalic delivery Brachial palsy Transient paraplegia*  
D McW was brought to the hospital at 5 weeks The eleventh pregnancy ended with a difficult delivery requiring forceps During the manipulations the right scapula was fractured After birth the right arm was completely paralyzed

When we examined her the right arm was held in the typical position of severe upper arm brachial palsy The left arm was rather stiff but not limited in motion The abdomen was distended, the legs moved very feebly and lay limply in abduction and external rotation at the hips, flexion at the knees and equino varus at the ankles No vigorous reflex activities were elicited No anesthesia was detected (fig 47)

We lost sight of the child for nearly 16 months At the end of that time she was walking and except for decided varus deformity of the right foot and limitation of elevation and abduction at the right shoulder, she seemed normal No signs of tract involvement were made out

*Comment* The brachial plexus injury was evident enough The coincident fracture of the scapula was proof that force had been used The interesting feature is the rapid recovery of strength after what seemed to be a widespread injury of the cord, largely, if not entirely, confined to anterior horn cells

*Case 23 Widespread involvement of the cord with unusual contractures*  
J T Z was admitted to the Out Patient Department in June, 1924, at 2 months

The breech delivery in a primiparous mother was difficult Respiration was established after an hour's work and no cry was heard for 4 hours For the next 2 weeks he was extremely weak, being fed with a dropper After this period it was observed that the abdomen was large, the arms stiff and awkward and that the legs did not move

We saw him at 2 months and during a period of 2 months more kept him under observation No important change occurred except for increasing use of the arms and lessened contractures of the legs

Physical examination showed constant but correctible turning of the head to the right No cranial nerve abnormality was observed The child seemed bright The arms were kept in the position shown in the photograph (figs 48 and 49) No complete paralysis of any muscle group





FIG 48 CASE 23

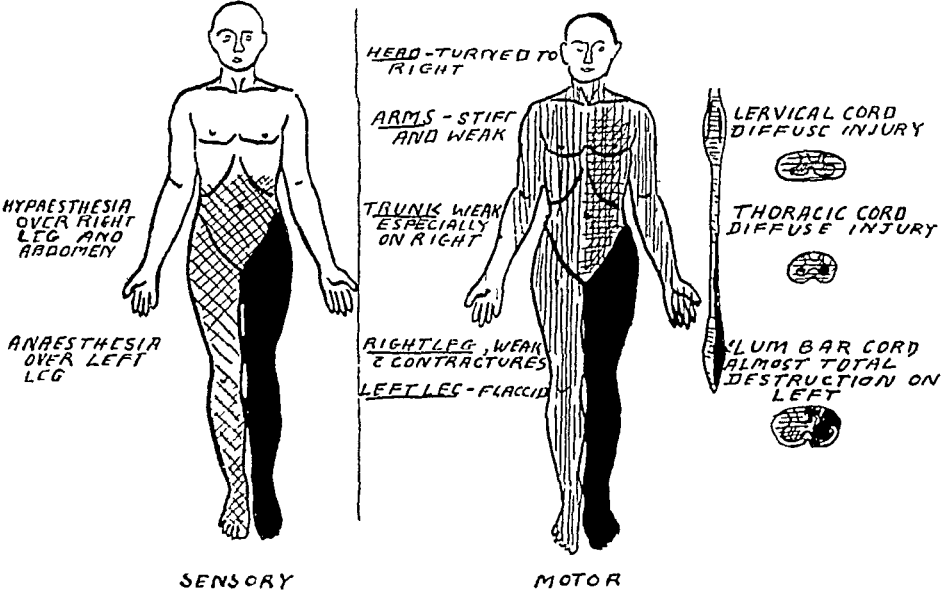


FIG 49 CASE 23

was made out but all motions were slight. The chest moved very little with respiration. The abdomen bulged, especially on the right. Feeble, ineffective motions could be seen in the left leg, none in the right.

On further examination both arms and the right leg were stiff, the left leg was flaccid. Obstinate contractures were present at the right hip and right knee.

Sensation was apparently abolished over the left leg and was very slight over the right leg and the whole of the abdominal wall. However, pricking over either leg led to evacuation of the bladder but not to the sharp reflex motions we have usually observed with urination.

*Comment.* The child certainly has a diffuse cord injury. In all probability a cord injury alone is responsible for his condition. It is, of course, arguable that he had in addition a cerebral injury accounting for the initial apnoea and an injury of the brachial plexus on the left. But only a cord lesion can explain the flaccid abdomen, the hypaesthesia and the anesthesia, and the flaccid leg.

The observation of most interest is that concerning urination. It is obvious, from a study of our other cases and of Head and Riddoch's papers, that elicitation of urination by nocuous stimulation of a flaccid limb is unusual. The only reasonable explanation, which is constantly suggested by these cases, is that the infant's nervous system, being very primitive and resistant to "shock," will exhibit reflex activity when comparatively small groups of physiological units are intact. In this case it is fair to assume that some impulses reach the cord from the leg in spite of gross anesthesia. In adults, and in most of our babies, the elicitation of urination by nocuous stimulation is usually impossible unless the lumbar enlargement is practically intact. The whole subject forms a fascinating field about which much could probably be learned from a more vigorous and detailed study of material like that reported in this paper.

The diagrams in this case, more than most of the others, represent in a rather unsatisfactory way our personal opinion. Obviously other interpretations are legitimate.

*Case 24. Diffuse injury with ataxia as prominent sign.* C. L., 5 years of age, was brought to the Orthopedic Out-Patient Department of the Children's Hospital October 24, 1925. The parents were not satisfied with his posture or gait.

The obstetrician had expected to do a Caesarian section, but maternal convulsions led him to do an accouchement forcé and version. The delivery of an 8 pound baby through the primiparous canal was remarkably difficult. Resuscitation was not required. However, examination revealed several fractured ribs and a fractured left clavicle.

At 15 months the child began to walk and talk. Ever since that time he has been awkward, unsteady, and generally incompetent physically, though bright mentally.

In the Out-Patient Department and later on in the wards, it was evident that the child presented a most confusing picture. In the first place he had definitely bad posture described by the orthopedists as follows:

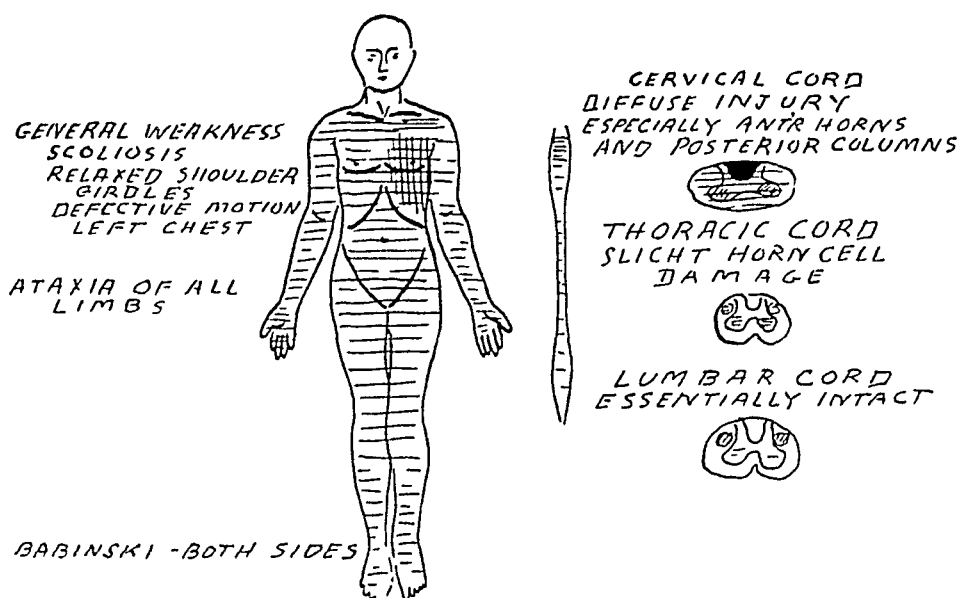


FIG 50 CHART OF CASE 24

"The child stands with his left shoulder and hip higher than right. There is a left lumbar dorsal scoliosis and slight upper dorsal cervical scoliosis to right. This scoliosis corrects by forward bending with slight amount of rotation of spine. General kyphosis of upper dorsal spine and increased lumbar lordosis. Chest shows a flattening of left side from first to tenth ribs. Right chest full. Abdomen prominent."

As he walked it was obvious that he was weak, unsteady and stiff. He tended to walk on his toes.

On detailed examination no disturbance of control could be found in the muscles of the head and neck. On the other hand, the control of all groups

of muscles of the arms, trunk and legs was disturbed. The most marked feature was generalized weakness, quite strikingly like that seen in progressive dystrophies, the shoulder girdle was loose and the arms decidedly weak. The trunk was flabby and the legs, though slightly stiff, were not strong. On getting up from a lying position he "climbed up himself" in the classical manner of dystrophic patients. There was no evidence of pseudohypertrophy.

In addition to weakness he had distinct ataxia demonstrated by the usual tests. The reflexes were all diminished and there was a definite Babinski sign on the left. No sensory disturbances beyond ataxia were discovered. The sphincters were competent (fig. 50).

Lumbar puncture revealed nothing abnormal. The pressure relations were normal and cytological and chemical studies negative.

A roentgenogram showed, in addition to the scoliosis, a spina bifida of the last lumbar and first sacral vertebra. This finding, of course, could hardly be regarded as significant in a child of five with the clinical picture presented.

*Discussion.* Any delivery involving fractures of several ribs and a clavicle can, of course, be considered as unusual. In this case the operator was a well known obstetrician fully aware of the dangers involved but forced to do an unexpected version on account of the mother's condition.

When the child was seen by us he showed weakness and ataxia with postural changes, as well as the minor detail of a positive Babinski on one side. The perversions of control suggest a diffuse non-selective and fixed pathological condition. To our minds the presumption in favor of a diffuse cord injury, chiefly involving anterior horn cells and posterior columns, is strong.

Dystrophy, at the stage of disability shown by this boy, is almost always accompanied by pseudohypertrophy. Moreover, it is progressive. Amyotonia is worth thinking of, but in our experience is not usually accompanied by scoliosis of this severity. Infantile paralysis and the like are almost excluded by the history. The normal spinal fluid findings pretty well exclude tumor and syphilis. The various degenerative conditions such as diffuse sclerosis are almost unknown in infancy. We therefore feel justified in including this case as one of obstetrical cord injury.

Treatment is, of course necessary. The scoliosis is perhaps the most important sign demanding attention. On the whole the future is not too gloomy. Great physical strength is not to be hoped for, but an active, relatively undeformed body is within the probabilities. Mentally, of course, he is not at all handicapped.

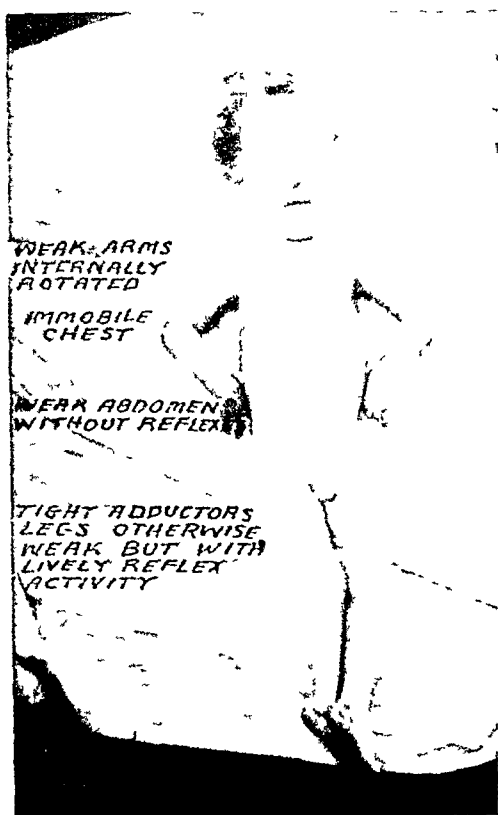


FIG 51 CASE 25

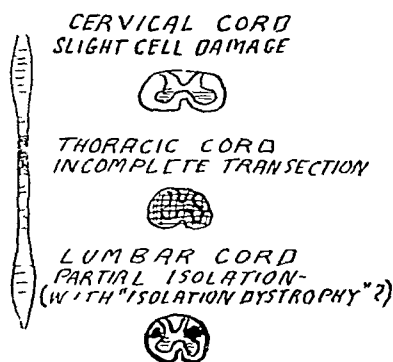


FIG 52 CASE 25

*Case 25* Diffuse injury with combination of flaccidity, spasticity and reflex activity. J T was brought to the hospital at 21 months on account of muscular weakness. He was an only child delivered after 2 days of labor by a difficult breech extraction. He breathed well at once. Mentally he was precocious, talking freely and well.

Weakness had been the dominant symptom from birth on. He held up his head at 6 months but had never sat alone. The intelligent and observant parents state that at first the arms were weak, abducted, externally rotated with fingers closed over the abducted thumbs. The arms felt

"tight" The legs had moved very little and the adductors had always been stiff

When we first saw him the situation was as shown in the photograph and the diagram (figs 51 and 52) The arms were internally rotated, flexed at the elbows and showed general weakness but no contractures The chest was immobile the abdomen weak and the legs limp with some contracture of the adductors Feeble voluntary movements were possible both in arms and legs The deep reflexes were absent throughout On painful stimulation of the legs strong and abrupt activity could be elicited No complete mass reflex was seen The contrast between the powerful reflex activity and the feeble voluntary movement was very striking No sensory abnormalities were made out

*Comment* This baby was delivered by an obstetrician of recognized standing There is no evidence of error of technique The first idea that occurred to us was that we were dealing with a double brachial palsy with cord injury, but the absence of contractures is rather against this view On the whole, the most logical explanation is that the upper thoracic cord was seriously injured with consequent impairment of anterior horn cells The feeble voluntary movements of the legs combined with tight adductors and strong reflex activities is consistent with this view Of course, later on it may be obvious that sensation, particularly muscle sense, is impaired As far as we could discover at 21 months no sensory tracts had been injured

*Case 26 Double brachial palsy Spastic paraplegia* I W was seen at 5 months in March 1924, and was followed for 4 months

The obstetrical history is unusual The mother was a multipara, without previous trouble The face presented This was changed to an occiput presentation by the obstetrician High forceps were used and the baby delivered with great difficulty The other details and the weight are not known

Resuscitation by hot and cold water was unsuccessful and swinging according to Schultze's method was finally utilized After respiration was once established the child did well, but moved its arms very little The left was the better of the two

On examination there was definite narrowing of the palpebral fissure on the left The face was moreover rendered asymmetrical by cicatricial tissue about the mouth due to cuts attributed to the forceps blades Nothing

else was abnormal above the arms. The arm weakness was slight (according to the mother this had improved steadily since birth). However, the right arm was held internally rotated and adducted. The activity of the left was slightly limited in adduction and the arm was usually pronated. The chief thing about the arms was the general weakness, the absence of contracture and the absence of deep reflexes.

The legs were moved freely but there was clonus at knee and ankle on both sides, Babinski phenomena on both sides and a definite crossing of the legs when the child was put on his feet. No sensory disturbances could be made out. At the first examination the trunk seemed normal.

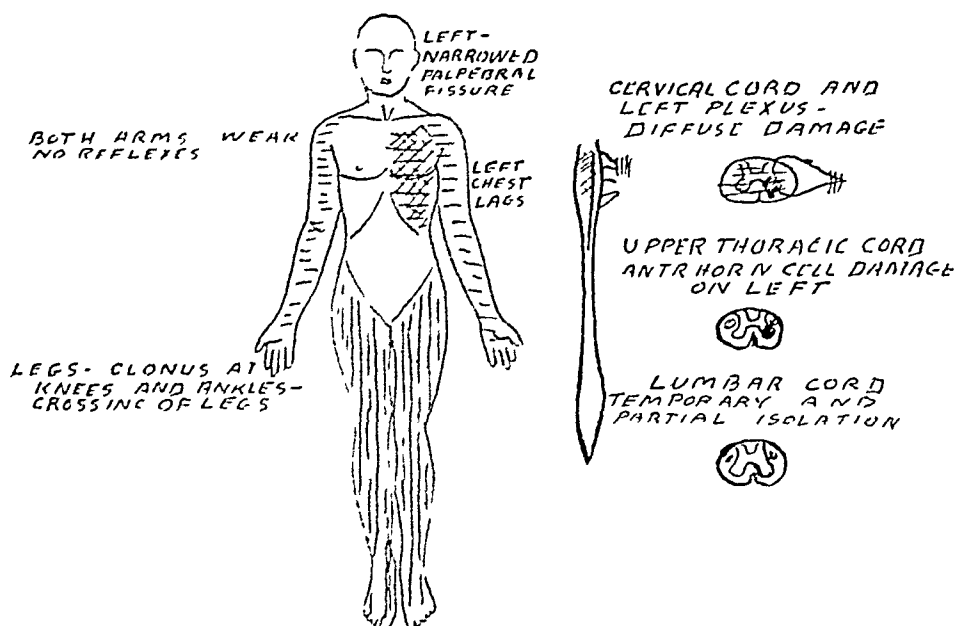


FIG 53 CHART OF CASE 26

At 10 months the picture had altered. The arms showed marked improvement. The chest showed marked lagging on the left. No signs of intrathoracic disturbance were found. In spite of complete absence of rosary or epiphyseal enlargement the ribs flared. The spastic phenomena which had been persistent up to 8 months had disappeared (fig 53).

*Comment* The weak arms without contractures suggest a cord rather than an isolated plexus injury. A sympathetic lesion on the left could explain the asymmetry of the palpebral fissures. The asymmetrical chest and the flaring of the ribs, in the absence of rick-

ets, suggest a rather diffuse lesion of the cord. Even in babies ankle and knee clonus usually indicate interference with cortico spinal impulses. The interpretation which seems to us most reasonable is partial avulsion of the brachial plexus with diffuse cord damage at about the fifth cervical segment. Clearly the prognosis in this case is excellent.

The exact mechanism here is in doubt. Swinging as a method of resuscitation is certainly vigorous and it is conceivable that the evident injury was due to it rather than to the stress imposed during delivery.

*Case 27 Severe injury of spinal cord after head delivery* D. R. O'N. was first seen at 3 months in December, 1922. The primiparous labor was not remarkable. The head presented, the baby weighed 6 pounds and 10 ounces. No history of traction could be obtained. Almost no movement of arms or legs had been noted up to the time she was brought to the hospital.

On examination the baby showed almost complete paralysis of both arms with extreme relaxation of the shoulder girdles so that the head of either humerus could be easily dislocated and replaced. Slight movement of the hands occurred. The trunk was weak, the left chest was immobile, and the abdomen soft. The legs were flexed and externally rotated at the hips, flexed at the knees and extended at the ankles. Detailed examination of the legs revealed fair power in the quadriceps, some strength of the posterior calf muscles, and great weakness of the rest of the muscles. Reflexes were not obtained at the first visit. Diminished sensation was noted over the whole right lower extremity.

For 2½ years we saw the child at intervals. The arms improved but were weak and the extreme relaxation of the shoulder girdles was still present. The retraction of the left chest persisted and a scoliosis developed. With support the child could walk a little but the legs were weak and the gait uncertain. No reflexes could be elicited on the right but on the left clonus and other evidence of spasticity was evident. Sensation was still defective over the right leg. The sphincters were competent. The child was intelligent (figs 54 and 55).

*Comment* A diffuse cord lesion with the most marked involvement in the lower cervical segments is the obvious explanation of the clinical picture. Isolated brachial plexus injury, as far as we know, almost





FIG 54 CASE 27

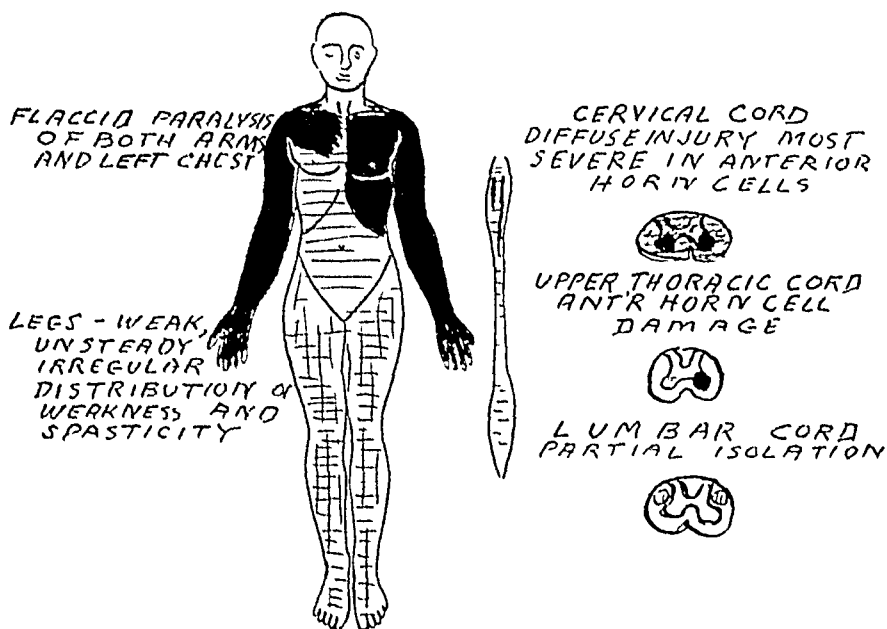


FIG 55 CASE 27

always results in some contracture about the shoulder. Congenital defects are conceivable, but no evidence of their occurrence is available.

In all probability a true avulsion of the brachial plexus occurred with hemorrhage into the cord. On the whole the injury was largely confined to anterior horn cells though the sensory disturbance over one leg and the spasticity of the other suggest a fairly diffuse lesion.



FIG 56 CASE 28

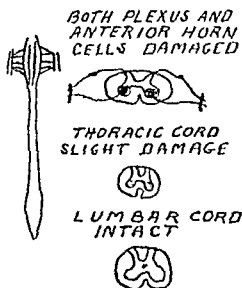


FIG 57 CASE 28

*Case 28 Bilateral flaccid paralysis of the arms.* P. S. was seen in April, 1924, at the age of 2 months. The mother was a primipara delivered by breech extraction. The child at delivery did not breathe and "looked blue and dead." With some difficulty it was resuscitated.

Complete flaccid paralysis of both arms was noticed at once and had persisted since. The baby had thrived and the photograph taken at 5 months shows a bright well nourished child.

When she was first examined the most striking feature was the total flaccidity of both arms including the shoulder girdles. No sign of con-

tracture was noted then or at any time during the 3 months she was under our supervision. In addition, both palpebral fissures were narrow and the pupils consistently small. The chest moved poorly and the retraction of the lower chest on respiration is well shown in the photograph (figs 56 and 57). The grooving of the lower chest was not apparently due to rickets of which the child showed no signs. The abdomen was soft but the muscles were by no means flaccid. Except for some adductor tightness the legs seemed normal. No sensory disturbances were made out.

No improvement took place in 3 months and exploration of the plexus was suggested but refused.

*Comment* The condition of the arms strongly suggests a double peripheral palsy of severe type. On this basis the narrowed palpebral fissures and the small pupils would point to sympathetic involvement. Pure peripheral palsy, even if severe, is almost always accompanied by unequal pull of the muscles of the shoulder girdle, some of which are not supplied by the part of the plexus which is exposed to stress and so do not share in the paralysis due to plexus injury. In this case the whole girdle was flaccid. Moreover the muscles of the chest are evidently involved. The completely symmetrical character of the injury and the total absence of improvement is unusual in peripheral injuries. Furthermore, the "asphyxia" in the absence of any signs of cerebral injury is explained by a cord injury.

The logical interpretation, in our opinion, is that the child suffered from true avulsion of the roots of the plexus. Avulsion of this type is probably always accompanied by injury of the cord as well. In this case the stress of the injury evidently fell upon the anterior horn cells leaving the tracts undamaged. The only possible chance lay in exploration of the plexus in the hope, which was unpromising, that repair would pave the way for some return of function.

#### THE LITERATURE

The earliest literature on birth trauma contains very little valid pathological or clinical data upon injuries of the spinal cord. In 1836 E. Kennedy in a paper on cerebral and spinal apoplexy in the newborn records the presence of abnormal congestion of vessels near the cord and of extradural spinal haemorrhage, but all details are lacking.

Little, in his classical paper on birth injuries mentions the spinal cord but gives few details

The only reference before 1870 which appears to bear directly upon injuries of the spinal cord is a treatise of Mauthner on "Diseases of the Brain and Cord in Childhood" published in Vienna in 1844. We have not been able to find the original but in an article by Litzmann a full abstract of pertinent facts is given. Two breech babies are mentioned with complete paraplegia. Apparently no details were given and no autopsies were done. However, Mauthner recorded the diagnoses as spinal apoplexy.

J. Parrot, in 1870, published a case report which is so important that we quote it practically in full. In addition he reported a second case in the practice of M. Gueniot which is worth study.

The first case was a female baby of  $6\frac{3}{4}$  pounds seen when 3 days old. Nothing abnormal had been noted up to that time, except jaundice.

The upper limbs, which remain completely inert no matter what stimuli are applied to the skin are in a state of total flaccidity and their articulations present striking mobility such as I have never seen in any other case. The skin of these parts is, however, not insensible and when one pricks it one provokes cries but does not elicit the least movement.

When the infant is lying on its back one cannot perceive any spontaneous muscular activity in the legs, but if the baby is held under the arms, the legs are held in a semi flexed position and limited but unquestionable movements occur.

Moreover, whatever the position of the little patient, if an attempt is made to extend the leg upon the thigh, a certain resistance is experienced, and if the skin is pinched the habitual flexion is immediately exaggerated in an abrupt manner (*d'une manière brusque*).

Two days later a note states that the condition is the same but adds

Since the patient entered the ward the bedding has not been soiled either by feces or by urine. This escapes at the moment when the thermometer is introduced into the rectum. No bile coloring, no albumen nor any sugar is found.

Death occurred on the seventh day of life.

An autopsy revealed cerebral hemorrhage. In addition the spinal

findings were recorded with great care. In the first place no gross vertebral damage was found. On the other hand, the meninges were torn almost across at the level of the sixth and seventh cervical vertebrae with complete divulsion of the spinal cord. The 2 ends were joined by a clot of blood which was intimately attached to them and filled the canal completely for some distance. As the meninges formed an incomplete sheath for this clot it might have been considered as cord substance covered with blood but was larger in diameter, soft in texture, looked like blood, and was flattened over most of its extent. It measured over 3 centimeters in length. The details of its gross appearance are carefully recorded and without question a physiological if not a complete anatomical transection existed. Below and above the lesion normal tissue was found. On the anterior surface at the level of haemorrhage some pia was intact with two pairs of nerves attached to it.

Parrot discusses with great thoroughness this case which was quite unprecedented in his experience. From the clinical and pathological data he came to the conclusion that the lesion must be due to abrupt force, in spite of the absence of external signs of violence. He then obtained the following history:

The mother was a primipara and the labor was difficult. The presentation being breech, great traction was exerted upon the feet. At a moment when the midwife was pulling with great force upon the left leg she heard a marked cracking sound [*cracquement très fort*] which seemed to come from a part still in the birth canal. She supposed it to be a fracture but a careful examination revealed no external evidence of any such accident.

For a quarter of an hour the baby was in a state of apparent death and was revived only after artificial respiration [*qu'en pratiquant insufflation*]. In the interval between birth and entrance to the hospital she did not cease groaning but no paralysis was noted.

The traumatic origin of the rupture of the spinal cord seems to us clear. It was caused by excessive traction, exerted upon the lower limbs while the upper part of the trunk was still engaged and was announced by the cracking sound so sharply appreciated by the midwife.

Let us examine the consequences.

The most immediate was the apparent death of the infant.

The saving of life and the taking up, apparently perfectly, of the functions necessary to life, in spite of the serious injury, are worth noting.

The child nursed and digested well, she breathed normally and her heart beat without appreciable difficulty.

The complete and remarkable flaccidity of the upper limbs is the consequence of the avulsion of the roots which share in the formation of the brachial plexus, and there is nothing in that which is not in accordance with what we know of the physiology of the nervous system, but what merits being emphasized is the apparent retention of function in the lower extremities,—and the proved retention in the legs of a sort of muscular tonicity which seems inconsistent with a complete rupture of the spinal cord.

We recall that the movements were extensive and rapid, that sensibility was retained and that if one supported the child by the shoulders the legs did not hang down at full length but were maintained in partial flexion and even had a momentary sort of flexion movement (*une sorte de mouvement de rappel vers le tronc*)

At the same meeting Parrot described a second case, reported by Guenot, of rupture of the cervical spinal column and the cord in a difficult version. An exceedingly narrow pelvis had required two previous versions, both resulting in living children. The head could not be brought through the superior strait without severe traction exerted upon the neck. The parietal bone was fractured. The baby was apparently dead at birth but was promptly revived. He lived 12 hours. "Obvious movements and even a certain agitation of the limbs were produced by the stimuli used to revive him."

At autopsy the body of the third cervical vertebrae was torn. There was a complete solution of the continuity of the spinal cord about 12 mm. below the medulla. There was also a cerebral haemorrhage.

We have read with care all the articles which we have found upon cord injury at birth. Although Parrot's name occasionally is recorded we have never seen any note suggesting that his contribution was important. Yet in the year of the Franco-Prussian War clear evidence was presented which proved facts of extraordinary physiological, pathological and clinical importance. The mass reflex in its typical form is admirably described. Cord injury with and without vertebral damage, with and without avulsion of the brachial plexus, is clearly recognized. As far as we know no one else has recorded active reflex activity below a transection in human beings within a few hours after injury.

We are not sufficiently familiar with neurological and physiological

history to judge the state of knowledge in 1870 but it is evident that Parrot, at least, was describing phenomena which were new to him. It is not possible to go into the successive steps which led in 1917 to the papers of Head and Riddoch. In general it is enough to point out that Bastian and Bowlby in 1891 were able to present clinical evidence which persuaded almost all clinicians that no reflex activity of any consequence could occur below a transection in man. It was not until 1917, 47 years after Parrot's paper, that Head and Riddoch, stimulated and encouraged by 2 generations of physiologists and with the almost unlimited material of the war hospitals for study, re-described phenomena which had been noted in a French journal in 1870.

Following Parrot's paper Nadaud recorded in 1872, in Paris, a breech baby with paralysis of all four limbs. The original contribution was not available and again we rely on Litzmann's abstract.

In 1873, Ahfeld presented a spinal column with evidence of injury due to extraction. He evidently regarded it as a curiosity and showed it with various pathological specimens at a meeting of the Obstetrical Society in Leipsic.

C. Ruge, in 1875, reported 64 deaths during or after breech extraction. In 8 he found rupture of the vertebral column.

In 1880, C. C. T. Litzmann published a detailed account of a baby with evident cord injury. The later examinations by Erb and the careful notes are of considerable interest. The child was still living at the time of the report. Litzmann's investigations into the fate of breech babies was continued for some time but he gained no direct evidence of other cases of cord damage.

In 1891, H. R. Spencer published an able analysis of cases of still-born babies. His statistical study and analysis of obstetrical procedures is well worth full quotation.

The spinal cord was examined in 44 cases only. In no case was there separation of the vertebrae.

In 5 cases the cord, membranes, and surrounding tissue were normal, in none of these was traction employed, three were apparently natural vertex deliveries, in one, version was employed followed by natural delivery, in one case the forceps was employed to hold the head in the pelvic brim, but not to deliver.

In 18 cases there was congestion or oedema

Congestion of the whole spinal cord was noticed in two

Congestion of the whole anterior cornua in three

Congestion of the whole surface vessels in seven

Congestion and oedema of the cellular tissue outside the theca in nine

In 30 cases there was haemorrhage

Outside the theca in twenty one

Between dura and arachnoid, two

Into arachnoid, six

Beneath pia (in one case dipping into anterior fissure) in three

Into the whole thickness of the cord in one

Into anterior cornua (two in lumbar, one in cervical, and one at various levels, but only one proved microscopically) in four

Into Goll's column in lumbar region in one

In 29 out of the 30 cases I have notes of the delivery

There were delivered naturally as cephalic cases six

There were delivered naturally as breech or footling cases, thirteen

There were delivered artificially by version (in all traction was employed), four

There were delivered artificially by forceps, four

There were delivered by cephalotripsy, two

To compare with this I give a table of the remaining 14 cases (in which the cord was examined and no haemorrhage found) Of these

There was delivered naturally as cephalic cases, ten

There was delivered naturally as breech or footling (one an easy breech lived two days), two

There was delivered artificially by version (no traction), one

There was delivered artificially by forceps (dead before applied), one

A comparison of these 2 tables, and the fact that, where haemorrhage was found, the proportion of normal cephalic cases to cases presenting by the lower extremity (naturally or by version) is as six to seventeen, whereas in all the cases examined the similar relation is as sixteen to twenty, shows that spinal haemorrhage is greatly favored by the presentation of the lower extremity. This is probably due partly to the greater compression undergone by the soft parts, and to the consequent driving of the blood to the central organs, and partly to the traction sometimes employed.

Microscopic examination of the medulla of case 104 (anencephalus) at about a quarter of an inch from the upper end, shows haemorrhage into the meninges, and numerous small haemorrhages scattered over the surface of the



section, the largest of these apoplectic foci is as big as a small pin's head. Examination of the *cervical cord* of the same case shows great congestion of the meninges and the escape of some blood into them. In the center of the section is a large focus of haemorrhage measuring a millimeter across, and there are several smaller foci scattered through the section. The haemorrhages have rendered the section very friable. Examination of the *lumbar cord* of this case shows great congestion of the meninges (the vessels in the anterior fissures being particularly full), great congestion of the substance of the cord, and a few small scattered extravasations. The whole of Goll's column is permeated with extravasated blood, the corresponding column on the other side being comparatively healthy. The large multipolar cells have the spaces around them dilated and occasionally filled with blood corpuscles, which sometimes press upon the cells and appear, in places, to have caused rupture of their processes.

In 1892, C. R. Burr described 9 cases of brachial palsy as *spinal birth palsies*. His argument was based on reasoning rather than on pathological data and attracted no particular attention. His idea was that the distribution of weakness and the course of brachial palsy was far more easily explained by a lesion in the cord than by peripheral injury. Of course later work on obstetric paralysis, notably that of A. S. Taylor, favors the conventional explanation of peripheral injury, but, as far as we know, Burr's paper is the first that made the suggestion that brachial palsies were related to injuries of the cord.

In 1895, Jolly presented a case before a Berlin medical meeting. The baby, at that time a few months old, had a symmetrical paralysis of the arms. The delivery had been complicated by manipulations which changed a face presentation into a vertex. Oppenheim, in discussion, suggested that the position duplicated that described by Thornburn after adult injuries of the cervical spine. It was agreed that spinal cord injury was likely.

In 1896, F. Schultze presented 3 cases of cord injury in the newborn with autopsies. In each case version and extraction had been performed. Diffuse injury was found in all, with multiple haemorrhages involving considerable areas. The pathological descriptions are clear and are worth careful study.

In 1901, C. Handwerck published an excellent pathological descrip-

tion of the findings in a 3 months old baby who had been delivered by extraction. The thoracic cord was almost entirely destroyed with numerous adhesions to the overlying meninges.

In 1902, Beevor reported an autopsy upon an infant with paralysis of one arm, the trunk and both legs, with corresponding anesthesia. The history told of a difficult breech extraction. A fracture dislocation of the third cervical with widespread destruction of the spinal cord was found.

A Couvelaire in two excellent papers published in 1903 and 1907 reported a series of 6 autopsies where cord injury as a result of dystocia was found. In only one was there gross injury below the phrenic nuclei. This child was a breech baby. In a second case, where the umbilical cord was tightly twisted about the neck, scattered small hemorrhages were found in various places, including the lower spinal cord. In the other cases, the hemorrhages in the medulla and upper cord occurred during head deliveries.

In 1909, T. Gott reported 2 new cases with autopsies from Pfaunder's clinic. Both children had been delivered with difficulty, in one case the husband, and in the other a midwife being the operators. Widespread paralysis and anesthesia was recorded in both cases. Autopsies showed diffuse destruction of the cord over many segments. Very few anterior horn cells were seen below the upper level of injury. The meninges were adherent. The article is supplemented by excellent microphotographs.

Czyzewitz, in 1909, reported vertebral damage after extraction.

R. Lawatschek, in 1911, recorded the history and autopsy of a breech baby 9 months old with flaccid paraplegia. The autopsy showed widespread destruction of the lower cord.

In 1911, Stoltzenberg reported from an obstetrical clinic the results of examination of the spinal column in babies dying of so-called asphyxia. She found that ruptures of the cervical spinal column occurred in nine out of seventy-five. Of these eight followed breech extraction. The cords unfortunately were not studied, but no gross injury was noted. However, over 10 per cent of all "asphyxial" deaths were accompanied by gross lesions of the cervical spinal column.

In 1913, O. Grone reported 4 cases showing isolated but important spinal meningeal hemorrhage. The deliveries were of various types.

and no vertebral damage was found though the author was familiar with Stoltzenberg's paper. On the other hand, definite haematomata were found extradurally within the vertebral canal and in three of the cases no other cause of death was found.

In 1917, E. Sachs reported 16 cases of rupture of the spinal column during extraction. The paper is particularly interesting since he discussed the question of responsibility from the obstetrical standpoint. Fourteen of the 16 cases were delivered by the chief of service or his first assistant and therefore the experience and judgment of the operator were those of recognized specialists. Furthermore he discussed in detail the technical points of obstetric procedure. Unfortunately no adequate neuropathological details were offered.

Laffont, in 1919, reported one of the few cases we have come across where the cervical dura mater was completely torn across. The photographs of the gross specimen are excellent but unfortunately no detailed report of cord pathology is included. The child showed clinical evidence of transection in the upper thoracic region.

E. Holman, in 1919, recorded a baby who had been delivered by version at 7 months. A definite dislocation low in the spinal column was found when the case came under his observation in a school for crippled children on account of deformities. Holman realized that such accidents were probably frequent and cites a case reported by S. Kleinberg as a dislocation of the spine. He points out that this case was also a breech baby.

In 1920, C. W. Burr, reported 2 cases of transection after extraction in one of which an autopsy revealed a transection extending from the fourth cervical to the first thoracic segments.

In the same year F. H. Kooy reported his findings in a 9 year old child with clinical evidence of extensive cord injury following extraction. He supplemented admirable pathological descriptions with adequate illustrations. The cord was destroyed in its lower part except for one ventral pyramidal tract. Into his discussion of the function of that bundle of fibers it is not necessary to go.

H. Langbein, in 1920, published a paper in which she reviewed atypical cases of brachial palsy. She observed that many cases, roughly 10 per cent, had a considerable involvement of the shoulder muscles and the chest, often with scoliosis. A large number of these

cases followed breech labors. Apparently she did not consider the possibility of cord injury and presented no autopsy or operative findings. The clinical description of the cases is admirable and the search for comparable cases thorough.

E. Friedman, in 1920, reported one case of flaccid paraplegia after breech extraction. This was the only case he found in going over the records of 2000 successive neurological cases at the Children's Hospital in Boston.

M. Warwick, in 1921, in a review of necropsies of new-born infants reported 3 fractures of cervical vertebrae with cord laceration out of 136 cases where the central nervous system was examined. Without much question the incidence of cord injury in this series is not entirely accurate as the routine did not involve complete exposure and sectioning of the cord. In a personal communication she states that all 3 cases were breech extractions.

In 1921, B. Crothers reported at a meeting of the New England Pediatric Society 5 cases of cord injury. Since these cases are mentioned in this article further abstract here is not needed. The cases were published in 1923.

In 1922, F. H. Leavitt reported one case of paraplegia due to extraction and appealed for general recognition of a condition which was not uncommon.

In the same year N. Capon reported 80 neonatal deaths. Ten were breech babies and of these four suffered injury of the vertebral column.

In 1923 R. N. Pierson reported the results of an investigation of deaths after breech extraction at Sloane Hospital in New York. His paper is a valuable contribution because like those of Spencer, Stoltzenberg and Sachs it describes the results of a considerable series of breech extractions under the adequate supervision of a recognized group of experts. The obstetrical situation is fully considered and careful notes are given.

From March, 1920, to September, 1922, in 142 viable babies in primary breech deliveries, natal or neonatal death occurred in 18 or 12 per cent. The incidence of breech presentation was 3 per cent. In 87 viable babies delivered by version and breech during the same period, natal or neonatal death occurred in 18 or 26 per cent. Version was never elective.

Spinal haemorrhage was noted in 17 or 47 per cent of the 36 cases; fractured vertebrae were found in 14 or 38 per cent

The only criticisms, from our point of view of this admirable review are the facts that the whole cord was not exposed as a routine and that sections were not examined

H Belfrage, in 1923, reported one of the few convincing cases in the literature of cord injury after head delivery The child,  $4\frac{1}{2}$  years old, was the second of twins and was a spontaneous occiput posterior delivery She showed sensory and motor changes from the second rib down and sphincter involvement Adequate laboratory and X-ray studies ruled out obvious defects of development and there is no reason to doubt the validity of the diagnosis

C O Kohlbry, in 1923, published a report with autopsy of a breech baby dying at 9 months His careful description of the situation at various ages is interesting Moreover early puncture showed yellow fluid with red cells, thus establishing the traumatic nature of the lesion Autopsy showed extensive sepsis of the urinary tract but in addition the cervical cord as far up as the specimen reached was a small column of tissue, apparently fibrous and adherent to the dura Below, it appeared normal Section of the cord at the site of the lesion showed complete degeneration of all tracts Below this level there was marked degeneration of the pyramidal tracts

Valentin, in 1924, reported an important case which is worth detailed report

A difficult version in a multipara was performed The head was hard to deliver and strong traction was needed Resuscitation by Schultze's swinging was used successfully

At 9 months, the child appeared well nourished The cranial nerves and eyes were normal The arms were held in abduction and elevated to slightly above the shoulder level The elbows were sharply flexed, the lower arms pronated and internally rotated, the fingers flexed and the thumbs adducted The only active movements were those of slight dorsi-flexion of the right hand and slight elevation of the right arm Passively all movements could be accomplished except for complete extension of the fingers Also, it was impossible to move the humerus without at the same time moving the scapula Sensation was ap-

parently reduced in the arms and no reflexes could be obtained. The legs showed nothing unusual except that the tendon reflexes were very lively, and Babinski's sign bilaterally positive. It was decided that the left plexus should be exposed by operation. This was attempted, but the child unexpectedly died during the operation.

At autopsy a well-marked condition of a status lymphaticus was found.

Both plexuses showed evidence of injury. On the left side the upper root was thickened and indurated just at the entrance to the spinal canal. On the right, the roots showed several thickenings, but less induration. Grossly the cord showed a diffuse swelling in the middle of the cervical region with dural adhesions on both sides of the cord for a distance of 2.5 cm. On the posterior aspect of the cord, extending from the cervical region downward, was a whitish zone 0.5 cm wide. This zone bordered on the region of the lateral pyramidal tracts which looked bluish gray in color. Histological study of the cervical cord showed the anterior median sulcus to be widened and filled with pial connective tissue. On the left side the anterior horn cells and surrounding white matter were replaced by connective tissue in which only a few root fibres could be seen. On the right, the anterior horns appeared normal but were bordered by some connective tissue. Except in the posterior tracts, the anterior pyramidal tracts and the periphery of the cord, there was a general loss of white substance. Below the cervical region there was an area of degeneration in the lateral pyramidal tracts, more on the left than on the right, which extended throughout the entire cord.

The evidence of coincident injury of cord and both plexuses is complete. Yet relatively slight evidence of the cord involvement had been made out on physical examination. It is also worth noting that the swinging could not be held responsible since the conventional technique of this terrifying procedure does not involve stress upon the brachial plexus.

In 1925 Ford reported 6 cases, one with autopsy from the Johns Hopkins clinic. These cases were quite comparable to some of those reported here, showing varied reflex activities. His autopsy report describes a sharply defined high thoracic transection with dural rupture.

E Harloff, in 1925, reported a case of flaccid paraplegia with dislocation of the fifth cervical vertebra after extraction. He regarded the fact that the child lived 9 days as remarkable.

As we went through the scattered cases reported in the literature it seemed obvious that the only reason cord injuries had not been generally recognized was that the condition had never been subjected to continuous investigation. Each author took up the subject as a matter of transient interest, reported a few cases and dropped it. For some curious reason the relation between traction and cord injury never received discussion in textbooks. The only adequate treatment is in Ehrenfest's monograph entitled "Birth Injuries of the Child" published in 1922.

The cord injuries themselves have not been completely studied in most series reported. Stoltzenberg's, Sachs' and Pierson's interest was focussed on vertebral damage. What is clearly needed to establish any valid notion of incidence is careful routine neuropathological examination of the entire cord after breech deaths. This type of research has been carried out, as far as the brain is concerned, by P Schwartz, R Beneke and E Holland among others. Cerebral trauma is clearly established. Yet in the many cases reported by these writers in their admirable papers, not a single cord injury was described, nor is there any suggestion that they were looked for. In certain papers such as Warwicks and Pierson's a certain amount of routine study of the cord is recorded, but no adequate exposure and section of the entire cord is reported.

In addition to the literature which bears directly upon birth trauma it is worth while to consider with some care a few of the classical papers upon the function of the isolated cord. Careful reading of Bastian's paper in 1891, which was responsible for establishing the erroneous conception that reflex activity in man was fundamentally different from that seen in animals, is decidedly profitable. Then in Sherrington's "Integration of the Nervous System" is a passage, which apparently put Bastian's assumption upon a firm basis. Sherrington says

In the monkey and in man spinal shock is not only peculiarly intense but peculiarly long lasting. The withdrawal from the isolated cord of influences

it is wont to receive from centres further headward may induce an alteration of trophic character in spinal cells—"an isolation dystrophy"—visible it may be as Nissl's chromatolysis. This "isolation dystrophy" ensuing on shock would add itself as a longer lasting, in some elements perhaps a permanent, depression. Certainly spinal transection is followed in the monkey by longer lasting "shock"—included in which I suspect is "isolation dystrophy"—than in other animal types observed in the laboratory. My results in monkeys bore out that which Bastian, Bowlby and Bruns, contrary to previous observers, have described as the typical condition in man after spinal injury completely severing the cord.

This weight of clinical and physiological authority practically eliminated discussion of the subject until 1917 when Head and Riddoch again established the fact that reflexes could be elicited below a transection. No abstract can do justice to these very important papers. The fundamental value of reviewing these contributions, in connection with the subject of this paper, seems to us to lie in the general moral to which they point. It is evident that the fallacy of Bastian's work lay in comparing seriously sick adult men with cleanly mutilated healthy animals. In so far as babies are concerned it is evident enough that Parrot in 1870 held the key to the situation when he reflected upon the primitive nature of the nervous system of the newborn.

In order to interpret certain phenomena it is worth while to read 3 or 4 recent papers which make certain points clear. Orr and Rows, in 1914, published a long paper reporting the findings after experimental infection near nerve trunks. They established the fact that persistent peripheral infection could damage the central nervous system. In this connection it is worth remembering that Head and Riddoch found that the activity of the isolated cord often subsided after infection became established.

The fact that the meninges are frequently torn renders it necessary to investigate the processes of healing. This subject is adequately considered in 2 papers by S. T. Harvey and his associates.

The relation of the cervical sympathetic to the brachial plexus and the cord is taken up by S. Cobb. His conclusions, based on study of war wounds, agree with our impression that injuries involving the



lower roots of the plexus are more likely to cause marked oculo-pupillary disturbances than injuries confined to the cord itself

## SUMMARY

### *I Etiology*

On the whole a study of the literature and a review of our own cases leads to the definite conclusion that most of the cases reported are due to the imposition of the unphysiological force of traction. Obviously in occasional cases the evidence is lacking, but there is no valid reason for concluding that asphyxia or generalized pressure are responsible in the atypical cases.

The problem is, therefore, a relatively tangible one. Most of the questions which make the subject of cerebral injury so complicated do not arise. Since traction upon a part of the foetus already delivered against the resistance of the part still within the birth canal is an entirely unphysiological procedure, it is evidently wise to determine the resistance of the tissues upon which it is exerted. The evidence upon this point seems to us quite clear. The most fragile and least elastic structures are the spinal cord, the membranes protecting it and the nerves issuing from it. As the force imposed is entirely under the control of the operator, it is incumbent upon him to realize that he is exerting it upon the nervous system and the membranes covering it as well as upon the strong and elastic tissues about it.

It is, of course, quite inadmissible for those who do not deliver babies, to lay down principles for those who deal with the emergencies of childbirth. On the other hand, owing to the concentration of babies injured at birth in our clinic, we are in a position to emphasize the fact that traction is an important source of disability.

The contrast between the almost complete silence of obstetrical text-books upon the danger and upon the unphysiological nature of traction, and the evidence which has accumulated is striking. We feel that, until writers of obstetrical text-books take up the control of stress upon the nervous system of the foetus as an important factor in successful delivery, accidents will occur in unnecessary numbers. We believe that the present serious situation can be corrected by careful revision of obstetrical teaching with increased emphasis upon the

methods of avoiding injury and decreased attention to asphyxia. From a survey of recent periodical literature we judge that certain obstetricians, notably Ehrenfest, agree with us.

## *II Pathology*

Two points are important. First, that the cord injuries are due to a type of force which can never be imposed except during labor. Even if traction is exerted upon the adult spinal column to the point of rupture, the result will hardly be comparable, for the rigid, closely articulated spine of older individuals supported by strong ligaments and powerful muscles is a very different structure from the elastic tube of the fetus. The nearest analogies are found in the unselective injuries inflicted by gunfire and the plexus injuries due to sudden blows on the shoulder. In neither case is force distributed over large areas.

The second point has to do with real but rather vaguely defined differences between fetal and adult tissues. It is sufficiently obvious from the case reports that the fetus can survive after extraordinary injuries have been inflicted. The absence of gross skeletal and muscular injury accounts in some measure for the surprising absence of "shock," but the primitive nature of the tissue must play a part.

It is not unreasonable therefore to expect diffuse and serious injury and that is exactly what we find. Instead of sharply localized damage we get lesions extending over many segments. In many cases, such as that reported by Parrot, we find babies surviving in spite of injury of the brain, the cord, and the plexus. Below the level of the most conspicuous injury we find diffuse cellular changes, perhaps as Sherrington suggests "isolation dystrophy," or normal tissue capable of independent activity.

On the whole we have an impression that the isolated cord of babies is resistant beyond that of adults. On the other hand, transient signs of activity may lead to unjustified hopes.

Since the meninges can be partially or totally torn across it is quite obvious that adhesions may occur which may cause interference with the circulation of spinal fluid or even totally obliterate the subarachnoid spaces. Meningeal trauma may, of course, occur without injury to the spinal cord. We have autopsy records of cases with definite

rents in the dura without cord injury If such cases should survive it is quite conceivable that later progressive signs might be observed

In general we believe it is reasonable to think of the situation as a unique one and not to be confused by failure to find analogies in adult diseases If the basic conception of a diffuse non-selective and essentially non-progressive pathological condition is borne in mind no great difficulties will be encountered

In a certain number of cases curious changes occur which suggest progressive pathological alterations For instance, in one of our cases a child exhibited temporary evidence of voluntary control In others reflex activity subsided after a relatively short time These changes are, at first glance, against our idea of fixed lesions However, there is evidence in Head and Riddoch's work which indicates that the viability of the isolated cord is low and that evidence of its physiological integrity may subside after infection Further suggestive work by Orr and Rows on the lymphogenous infections of the cord following sepsis in neighboring areas is interesting in this connection

Several points should be borne clearly in mind in planning any pathological investigation The incidence of cord injury in babies who survive the neonatal period can probably be established by clinical studies, and by the type of intermittent pathological scrutiny which has been reported in the literature On the other hand, the still-born babies and those who die in the first days should be investigated with particular regard to the possible results of obstetrical force If traction has been exerted the plexuses should be exposed and the cord sectioned after hardening The present situation is unsatisfactory The most cursory reading of pathological studies on the new-born reveals amazing discrepancies Holland, for instance, finds that 75 per cent of his breech deaths showed ruptures of the dural septa within the cranial cavity, Pierson that 38 per cent show ruptures of the vertebral column, Schwartz, in a long series of autopsies, finds that the majority of his cases have intracerebral lesions Clearly the next step is to recognize that many babies have injuries at various levels This fact was known in 1870, but has not been consistently borne in mind The clinical evidence indicates that diffuse injury is common and that any part or several parts of the nervous system may suffer The next step is to find out, by thorough patho-

logical investigation, whether the correlation between force and certain types of injury is as definite as it seems

### *III Incidence*

The ratio of cord injuries to other birth traumata or suspected birth traumata seen in our clinic and in private practice is perhaps suggestive. In the six years covered by this report, among new admissions, the definite cord cases in hospital and in private practice, excluding the two not seen by us, numbered 26, the uncomplicated brachial palsies numbered 216 and cerebral palsies where birth injury seemed a fair explanation 260. These figures, of course, are given with all sorts of reservations and are simply stated as an indication of the type of material at our disposal.

Various methods can be used by those with statistical enthusiasm to formulate figures from the literature. Insuperable difficulties seem to us to exist. On the whole, no completely satisfactory series of autopsies is available. As far as clinical cases go, there appears to be no way of knowing what proportion of all deliveries in a given place and period they represent. Until some adequate study, comparable to those available for cerebral injuries, is made it will be impossible to state the problem in any profitable way in figures and legitimate questions will remain unanswered. We, from a study of disabled children, believe the situation is serious.

### *IV Clinical considerations*

From our own standpoint the most interesting result of this study has been an increasing respect for physiological methods. As laboratory preparations, following mutilation of the central and peripheral parts of the nervous system, the cases present soluble problems. Every effort to arrive at correct conclusions by conventional neurological technique was blocked by the age of our patients and by the chaotic state of the conventional reflexes in infancy. The fact that we had to rely upon posture, activity, gross sensory changes and so on led us to use methods ordinarily confined to laboratories.

Often the diffuse nature of the lesions made accurate focal diagnosis difficult and relatively futile. On the other hand, we kept constantly

in mind that the management and the future of these children depended upon the intact physiological residue rather than upon the exact anatomical nature of the lesion. Looked at from this point of view the babies whose injuries were confined to the plexus and the cord had two assets of priceless value. The medulla and the cerebral cortex were intact. Most of them, therefore, could be expected to live and to be intelligent. In addition no important skeletal damage was usually present.

Moreover, we have come to believe that time-tables based on study of adult injuries are of no great value in forecasting the future of babies injured at birth. While we are not prepared to defend any hypothesis that regeneration of the completely divided spinal cord is possible, we have not enough respect for our own diagnostic acuity to enable us to state definitely that evidence of voluntary control of activity may not appear for the first time some years after birth.

Under these circumstances we believe that the sensible procedure is to make first of all a physiological survey. In this, we try to discriminate between abolition of function due to destruction of anterior horn cells, or nerve roots, disturbances of function due to partial interruption of tracts and uncontrolled reflex activity dependent upon an isolated part of the cord. The deformities due to absence or perversion of control are managed as well as may be. The bladder and the intestinal tract are considered and appropriate measures taken. In our experience catheters have not been necessary. The possibility of ulceration of the skin demands constant vigilance.

The least favorable cases, of course, are those with physiological destruction of the lumbar enlargement. In these cases urinary sepsis and trophic ulcers make it difficult to maintain life, to care for the children and to fit apparatus.

The children with apparently complete transections above the lumbar enlargement can be helped a great deal. The intermittent emptying of the bladder can be controlled in a fairly satisfactory way by utilizing the "mass reflex." The elicitation of this reflex by pinching the leg empties the bladder before it would otherwise contract. The absence of skin lesions makes it possible to fit apparatus.

The innumerable abnormalities due to partial injury present no insoluble problems to the resourceful orthopedist. The methods

must of course vary. On the whole, we believe that conservative methods should be tried first and we agree heartily with those orthopedists who believe that definitive operations, involving bone, muscle or nerve destruction, should be used as little as possible in young children. Physiotherapy can usually control contractures leaving the question of surgical attack to be taken up later on.

Differential diagnosis depends more than anything else upon a willingness to look at the problem of diagnosis from a physiological standpoint. The usual method, supported unfortunately by considerable emphasis in teaching, is to mass a collection of signs and symptoms and then to see what syndrome described in books best fits the situation. Clearly some cases will come close to "amyotonia congenita," others can be considered as "congenital scoliosis," "Infantile paralysis," "congenital atresia of the cord," and so on, are convenient pigeon holes.

The use of the word "congenital" should be clearly defined. We have a conviction that it should imply a defect in development. This conviction is not based upon our classical lore, for we see that it cannot be defended on etymological grounds. In fact the whole subject of defining the terms used in describing events from the beginning of labor to the initiation of independent respiration is clearly in need of consistent and authoritative revision. In any case where a baby shows signs of neurological interest immediately after birth the question of whether the cause antedated labor is interesting and of some importance. In a few cases we have seen children with disabilities somewhat comparable to those described here where atrophy was clearly prenatal. In many cases, of course, coincident abnormalities such as spina bifida and so on were found. Our general impression is as follows. Most prenatal defects of the nervous system run fairly true to type and are usually accompanied by tangible evidence that they have existed for some time. Children with birth trauma, on the other hand, usually present evidence which suggests a sudden interruption of function in a normally developed child.

In cases seen later in infancy and childhood we have simply relied on a good history, a physiological point of view, and a perhaps too emphatic distrust of syndromes. The most important thing is to

avoid the distressing mistake of classifying these cases as due to progressive disease

The condition which has given rise to the most serious doubts has been that of cerebral injury We realize fully that certain cases described here may be suffering from cerebral rather than spinal injury Even in adults with single lesions the problem of differential diagnosis is puzzling at times There is, of course, no reason to be sure that we have not misinterpreted signs, or indeed that the same child may not have injuries of the cord, the plexus and the brain We have tried, however, not to confuse this series with cases where doubts arise

#### CONCLUSION

Injury of the spinal cord due to obstetrical accidents is an important cause of disability It should be considered whenever the signs suggest that a diffuse, non-selective and fixed lesion of the cord is responsible for disability of the child On the whole, injured babies can be studied more satisfactorily by the methods used in the physiological laboratory than by attempts to interpret confusing tendon reflexes, fine sensory changes and other phenomena which are indispensable in adult practice

Though no discrete syndromes can be established our cases fall, in general, into a few groups Some show flaccid paraplegia, apparently due to almost complete destruction of the lower cord A second group exhibit lively reflexes dependent upon the isolated part of the transected cord, while a third are handicapped by disturbances due to perverted control as a result of partial destruction of afferent or efferent tracts Obviously coincident injury of the brachial plexus or of the brain will produce variations which may be confusing

The injuries, in almost all cases, appear to follow the application of traction during delivery The striking contrast between the apparent incidence of injury and the almost total ignoring of the subject by writers of obstetrical text-books justifies us in suggesting that a definite shift of emphasis is desirable Our contribution is simply the latest of a consistent series which have appeared at short intervals since 1870 If our interpretation of the facts is correct, cord injuries are usually due to deliberate imposition of unphysiological force upon

various structures of which the most fragile, the least elastic and the most important are the nervous system and its protecting membranes. If no adequate warning is given by teachers that traction is dangerous, the individual practitioner cannot be blamed if he uses it to the detriment of the babies he delivers.

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## IODIN IN THE TREATMENT OF DISEASES OF THE THYROID GLAND<sup>1</sup>

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*New York*

Iodin in one form or another has been used unknowingly from the earliest times in the treatment of goiter. The beneficial effect on goiter of substances now known to contain iodine is said to have been known to the Chinese fifteen centuries before Christ. Of these iodine containing substances, sponge ash is the best known, and was extensively used at the time of Hippocrates. In addition to its use by the Greeks as an important remedy in the treatment of diseases in general, Dioscorides specifically mentions the use of sponge ash in the treatment of goiter. Galen and Pliny also refer to its use. Humbolt (1) in 1824 described the occurrence of endemic goiter in the United States of Colombia, and refers to the interesting fact that these people knew one salt deposit was more beneficial than another. A young French physician, Roulin (2), came to Colombia after graduating from the University of Paris where he had learned of Coindet's work on iodine in the treatment of goiter. He became interested in this subject, and had analyses of these salts made for iodine by Bous-singault and found that the deposit containing the most iodine was the one which the natives had found most useful.

Another very interesting reference to the use of iodine unknowingly in the treatment and prevention of goiter is given in Mrs. Lucy Crawford's "History of the White Mountains" (3). After referring to the frequency of swelling of the thyroid gland in Coos County, New Hampshire, at the close of the seventeenth century, she relates that her grandfather brought sea-salt, a bushel at a time, 80 miles over the mountains on his back. She states that it was generally believed by the early settlers that the swelling of the thyroid was due

<sup>1</sup> Read before the American Climatological and Clinical Association meeting, Washington, D C, May 5, 1925

to the almost exclusive use of meat (deer, moose and other game) which the nature of the country necessitated, together with the lack of salt. They noted that children were more susceptible than adults and recommended that they be given larger quantities of salt, particularly if it was impossible for them to live near the sea a part of each year. This account clearly establishes the fact that long before the discovery of iodine our early settlers knew the value of sea-salt (for this was the only salt available) in the treatment and prevention of goiter. They also were aware of the fact that a diet consisting largely of meats was a potent cause of thyroid enlargement.

Iodine was first knowingly used in the treatment of goiter by the Geneva physician Coindet (4) in 1820—nine years after its discovery and isolation by the French chemist, Courtois (5) of Dijon. Within a year after its introduction as a remedy against goiter by Coindet, untoward effects were noted in certain classes of cases. These untoward effects were vividly described by Gairdner (6), who noted that “peculiar great and persevering anxiety, depression of spirits, emaciation, diarrhea, tremor, and nervous excitement simulating chorea” were produced in certain individuals. This symptom-complex was designated “Iodine Basedow’s” by Kocher (7), some seventy-five years later. These early observations on the untoward effects of iodine started a controversy which has now continued for more than a century, whether iodine should be used in the treatment of any form of goiter. There have always been supporters on each side of this controversy. Up to about 1890 the balance of medical opinion seemed to favor its use in small doses. Then due to the influence, particularly of surgeons under the leadership of Kocher, and to the overuse of desiccated thyroid introduced in 1891, the pendulum began to shift the other way. Since 1910, however, there has been a gradual return to the older views. This return to the use of iodine has been in great measure due to the rational application of the great mass of physiological facts acquired by and since Baumann’s discovery in 1895 of the normal presence of iodine in the thyroid. The gist of all this recent research as applied to modern therapy may be summed up in one sentence—that the thyroid requires an exceedingly small amount of iodine for the carrying out of its function, which so far as we now know consists in the elaboration

of an iodine containing hormone first suggested by the discovery of Baumann and isolated in crystalline form by Kendall in 1914. Undoubtedly the use of massive doses of iodine was the major factor in bringing iodine into ill repute in the earlier empiric treatment of goiter. And if one may draw a conclusion from the recent literature and from my own experience this is still the major cause of untoward effects. All the facts at present known support the view that minimum amounts of iodine are required for the normal physiological needs. Only three of these facts need be mentioned in illustration: (1) That 25 mgm. of iodine represents about the maximum storage capacity of the normal human thyroid. (2) As shown by Marine and Lenhart, 1 mgm. of iodine given at weekly intervals by mouth will prevent thyroid enlargement in dogs living under conditions which would otherwise produce thyroid enlargement. (3) As shown by Boothby and Sandiford, 1 mgm. of thyroxine may exert its accelerating effect on metabolism in man for as long as seventy days. With this general background in mind, what would seem the most rational plan of applying these and kindred physiological facts in the treatment and prevention of goiter?

For the sake of simplicity and, in my opinion, accuracy and clearness as well, we may group the diseases due to functional disturbances of the thyroid as follows:

I. Thyroid insufficiencies

1. Simple goiter (endemic, sporadic, epidemic, etc.)

2. Myxedema

a. Infantile (cretinism)

b. Adult (Gull's disease)

II. Graves' disease

SIMPLE GOITER

The most recent view of the etiology of simple goiter assumes that it is a work hypertrophy depending upon a relative or an absolute deficiency of iodine. The causes of this deficiency may be grouped under three headings:

1. Factors which bring about an abnormally low intake as is known to occur in districts of endemic goiter. The normal source of iodine

is mainly from food and water and it has been abundantly shown, first, by Chatin (8) in 1852 that the food, soil and water are deficient in iodine in districts of endemic goiter. It has also been shown that thyroid enlargement may be induced by the experimental deprivation of iodine. It may be accepted, therefore, that an absolute deficiency of iodine is one important cause of endemic goiter.

2 Factors which divert an otherwise adequate supply of iodine. This is purely hypothetical at present. It is conceivable, however, that intestinal bacteria or parasites might divert to their own use or prevent the absorption or utilization of an otherwise adequate supply.

3 Factors which temporarily increase the needs of the organism for the iodine containing hormone, that is, factors which create a relative insufficiency. Among the most important of these are: (a) Diet, as shown by the production of goiter in brook trout on a diet of pig's liver or in pigeons on an excessive diet of lard or other iodine free digestible fat (McCarrison), (b) infections, as in pulmonary tuberculosis, syphilis, tonsillitis and focal infections, (c) pregnancy; (d) puberty, and (e) Graves' disease.

The first group depends upon a definite, simply defined and easily understood factor, an actual deficiency in iodine, whereas the third group which depends upon a relative or temporary insufficiency is more difficult to define, less understood and by far the most important, since no living animal with the ductless thyroid is ever free from the possible influence of one or another of the factors enumerated. These factors of diet, pregnancy, puberty, infections, etc., are active in goiterous as well as in non-goiterous districts, and when combined with a real iodine starvation the effects are exaggerated. As will be pointed out later it is important to distinguish between groups 1 and 3 when planning or evaluating treatment. Emphasis on the iodine deficiency has been so prominent of late that we are liable to overlook more important elements in the treatment particularly in the so-called sporadic goiter.

#### PREVENTION OF GOITER

The principle of prevention depends upon the fact that if the iodine store in the gland is constantly maintained above 0.1 per cent, dry weight, no enlargement occurs.

Simple goiter may be easily prevented in man by the administration of 1 mgm, and possibly less, of iodine daily. Iodine in any form and administered in any manner is effective. This fact introduces difficulties and advantages—difficulties regarding the selection of the best form and manner of administration, and advantages in that the desired result may be accomplished with certainty in a great variety of ways. The amount of iodine necessary and the ideal plan of administration for such purposes have not yet been worked out. The most effective means, and to my mind the least objectionable, would be the use of a salt containing 1 mgm of sodium or potassium iodide per each 10 grams of salt, that is 0.01 per cent. Such a plan would provide universal prophylaxis at a nominal expense. Where small units of population are to be protected, as for example school populations, iodostarin or starch-iodine tablets containing 5 to 10 mgm administered once a week may be used. Such a plan could also be readily applied by physicians in the prevention of thyroid enlargement during pregnancy and lactation. Iodine may be introduced periodically into the drinking water following the plan first used by Marine and Lenhart in 1910 in preventing goiter in brook trout. For this purpose iodine in a concentration of one part per million for a period of 2 weeks each autumn and spring would seem ample. In individual cases in private practice syrup of hydriodic acid is a very convenient and easily obtained form for administration. One or 2 ounces twice each year is ample. Desiccated thyroid also completely protects the thyroid against enlargement, but is too dangerous a drug to recommend for this purpose.

Much has been written about the danger of causing or of aggravating Graves' disease by the use of iodine. The use of iodine in the amounts above recommended (i.e., not more than 1 mgm per individual per day) in the prevention of goiter is in my opinion not associated with any noteworthy dangers. Occasionally iodism may be observed and some authors have claimed that this can be prevented or lessened by the use of calcium iodide. It is of such rare occurrence that attempts to administer iodine in a form which would not cause iodism may be neglected until the susceptible individuals have been discovered. It is possible, though improbable, that cases of early Graves' disease may be aggravated by the administration even of

these small amounts of iodine. Most, if not all the instances of the alleged production of Graves' disease by the use of iodine that have appeared in the literature and all that have come under my observation have occurred in *predisposed* individuals and have been due to *the gross abuse of iodine* or desiccated thyroid alone or combined. To illustrate from personal experience, of 53 goiter cases seen during the past nine months all but two stated they had taken tincture of iodine, Lugol's solution or iodine in other forms in amounts equivalent to 200 to 300 mgm daily for several weeks.

#### TREATMENT OF GOITER

Regarding the use of iodine in the treatment of thyroid enlargements we cannot be so dogmatic as in the case of prevention. When the treatment can be instituted in the early stages of development of the thyroid enlargements of endemic goiter districts the methods and the amounts of iodine recommended for prevention bring about a cure. In our Akron experiment where 2 grams of sodium iodide were administered over a period of two weeks twice yearly for prophylactic purposes 773 thyroids out of a total of 1182 with enlargement showed reduction. Similar results have been reported from Switzerland by Klinger and others and from Italy by Pighini. In sporadic goiter the cause of the relative or temporary thyroid insufficiency (infection, diet, etc.) must be sought for and corrected if iodine therapy is to be of permanent value. In the long standing cases no plan of medical treatment can with certainty accomplish more than relieve any existing functional insufficiency. In these cases the functional insufficiency is usually already relieved or outgrown and the patient seeks the physician's advice largely for the correction of the cervical deformity. Occasionally striking curative results are observed even in long standing cases. In such cases the thyroids are anatomically in the hyperplastic, simple or colloid form, free from hemorrhages, cyst formation, calcification or adenomata, so characteristic of long standing human goiter. Whether a curative effect is produced or not, and certainly if the individual expects to seek surgical intervention in the event of failure of medical treatment, iodine should be given. The best plan of medical treatment in my opinion requires the administration of standard U.S.P. desiccated thyroid in 0.1 to 0.2 gram doses.

daily for a period of two weeks, and if there has been no change in pulse rate, loss of body weight or other evidence of injury, the same treatment may be repeated. Then after an interval of one to two weeks some form of iodine, as for example syrup of hydriodic acid in 2 to 4 cc doses daily, should be given for a period of two or three weeks. This combined treatment with desiccated thyroid and iodine may be repeated three times during the year, and for the maximum reduction, at least a year is required. Desiccated thyroid unquestionably causes a greater reduction in the volume of the thyroid and more rapidly than does iodine. The administration of large amounts of iodine suddenly often causes the thyroid in about seven days to become very firm to the touch, painful and clinically even larger than before its administration (the so-called iodine thyroiditis of the literature). This is due to the rapid accumulation of colloid in the alveoli which iodine induces.

The untoward effects of the excessive use of iodine or desiccated thyroid in the treatment of goiter are real and often serious. Comdet in 1821 first noted these effects in certain types of goiter and Gardner as above mentioned in 1822 observed and described all the essential features as we know them today. This effect of iodine is most commonly seen in women with long standing goiter during or after the menopause which is in some unknown way a factor in causing the increased susceptibility.

#### EXOPHTHALMIC GOITER

In sharp contrast to simple goiter we know almost nothing concerning the etiology of Graves' disease and until this is known a rational therapy cannot be expected. The prevailing opinion now favors the view that Graves' disease is not primarily a thyroid disease but is in some way dependent upon a deranged function of the visceral nervous system. This view is only a return to that held by the older internists and neurologists, including Charcot, Trousseau, Buschan, Gowers, prior to the introduction of the Gauthier-Moebius hypothesis in 1886. My own view is that underlying the typical clinical picture of Graves' disease there is a long standing constitutional anomaly which may be acquired or inherited (congenital), the acquired form coming on usually in association with or after the meno-



pause, the thyroid hyperactivity being secondary and a result of a powerful stimulation either through the sympathetic nervous system or through the blood stream or both. To determine the origin of this stimulation of the thyroid, as well as that of other tissues, particularly the lymphoid (thymus and lymph glands) is the major problem in connection with this disease. After a careful study of the literature together with observations and experiments on a large series of their own cases, Marine and Lenhart (9), (10), (11) came to the conclusion in 1910 that the thyroid reaction in Graves' disease was in no way different from that seen in other clinical associations. To quote

There were eleven cases in which the patients were treated with iodine from one to three weeks prior to operation. In all of the cases the iodine contents of the thyroids were markedly raised and in none had complete involution to the colloid state occurred. There were four cases which had received iodine for periods varying from two months to eighteen months and in all complete involution to the colloidal state was present at the time of operation. We can therefore reasonably conclude that the active hyperplasia of exophthalmic goiter has the same characteristic of rapidly taking up iodine that characterizes all other active functional thyroid hyperplasias and also that iodine induces a similar series of morphological changes in the exophthalmic goiter hyperplasia as in other active thyroid hyperplasias, and that these changes are histologically identical with those occurring in spontaneous involution (recovery).

From these studies we concluded "the essential physiological disturbance in the thyroid in exophthalmic goiter is insufficiency, its reaction compensatory and its significance symptomatic." Oswald (19) in 1902 and A. Kocher (20) in 1912 also fully described the effect of iodine administration in Graves' disease.

We are, here, concerned more particularly with the use of iodine in the treatment than with experimental data. Its beneficial effects are limited while its injurious effects are serious. The value of iodine is limited to relieving any real or relative insufficiency of the thyroid. This iodine undoubtedly does, but unless and until the cause of the thyroid stimulation which produces the relative or temporary insufficiency can be relieved no lasting benefit occurs merely from supplying the means with which the thyroid can manufacture more thyroxine more easily or more quickly. As above mentioned, Coindet in 1821

noted untoward effects from large doses of iodin in certain types of cases and Gairdner in 1822 definitely described the symptoms of Graves' disease in connection with his observations on the untoward effects of iodin in certain cases of goiter at least thirteen years before Graves recognized the syndrome. From the earliest literature on exophthalmic goiter, more than one hundred years ago, just as today, distinct benefit has been reported from the use of iodin. On the other hand highly injurious effects have been noted. A great increase in the injurious effects has been noted since the introduction of desiccated thyroid into goiter therapy in 1891. These effects became so serious that many of the ablest students under the leadership of Theodore Kocher opposed the use of iodin in any form in this disease, indeed in any form of goiter. Beginning about 1910 the pendulum began to swing back again to the view of the earlier observers, namely, that iodin could be used without danger if administered in doses somewhat approximating what might be called physiological (1 mgm daily). Why some patients undergo remarkable improvement and others do not is not understood. Patients with Graves' disease getting iodin even in small doses should be under hospital or other means of daily control. With this safeguard it is my opinion that every case should be treated with iodin in doses not greater than 1 mgm daily over a period of at least two months. The older observers used much larger doses than this as in the case of the recently much quoted therapeutic accident of Trousseau, who through mistake gave iodin instead of digitalis. Much more to the point are the numerous references in the literature to the deliberate administration of iodin in Graves' disease. Thus Cheadle (12) in 1869 reported 9 cases of true Graves' disease, showing "immediate and extraordinary improvement" in 2 cases and no injurious effects in the other cases. These effects he pointed out could hardly be referred to as a coincidence. Although the prevailing opinion at that time was that iodin always was injurious in Graves' disease, this observer regularly recommended its use in all cases. In 1875 Cheadle reported a second series of 6 cases, one, a very severe case, showed great improvement during the first two weeks of iodin administration and then relapsed. This case illustrates very vividly the outcome which is so frequently seen today. Cheadle concluded his paper with the following state-

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From these studies we concluded "the essential physiological disturbance in the thyroid in exophthalmic goiter is insufficiency, its reaction compensatory and its significance symptomatic." Oswald (19) in 1902 and A. Kocher (20) in 1912 also fully described the effect of iodine administration in Graves' disease.

We are, here, concerned more particularly with the use of iodine in the treatment than with experimental data. Its beneficial effects are limited while its injurious effects are serious. The value of iodine is limited to relieving any real or relative insufficiency of the thyroid. This iodine undoubtedly does, but unless and until the cause of the thyroid stimulation which produces the relative or temporary insufficiency can be relieved no lasting benefit occurs merely from supplying the means with which the thyroid can manufacture more thyroxine more easily or more quickly. As above mentioned, Coindet in 1821

noted untoward effects from large doses of iodin in certain types of cases and Gairdner in 1822 definitely described the symptoms of Graves' disease in connection with his observations on the untoward effects of iodin in certain cases of goiter at least thirteen years before Graves recognized the syndrome. From the earliest literature on exophthalmic goiter, more than one hundred years ago, just as today, distinct benefit has been reported from the use of iodin. On the other hand highly injurious effects have been noted. A great increase in the injurious effects has been noted since the introduction of desiccated thyroid into goiter therapy in 1891. These effects became so serious that many of the ablest students under the leadership of Theodore Kocher opposed the use of iodin in any form in this disease, indeed in any form of goiter. Beginning about 1910 the pendulum began to swing back again to the view of the earlier observers, namely, that iodin could be used without danger if administered in doses somewhat approximating what might be called physiological (1 mgm daily). Why some patients undergo remarkable improvement and others do not is not understood. Patients with Graves' disease getting iodin even in small doses should be under hospital or other means of daily control. With this safeguard it is my opinion that every case should be treated with iodin in doses not greater than 1 mgm daily over a period of at least two months. The older observers used much larger doses than this as in the case of the recently much quoted therapeutic accident of Trousseau, who through mistake gave iodin instead of digitalis. Much more to the point are the numerous references in the literature to the deliberate administration of iodin in Graves' disease. Thus Cheadle (12) in 1869 reported 9 cases of true Graves' disease, showing "immediate and extraordinary improvement" in 2 cases and no injurious effects in the other cases. These effects he pointed out could hardly be referred to as a coincidence. Although the prevailing opinion at that time was that iodin always was injurious in Graves' disease, this observer regularly recommended its use in all cases. In 1875 Cheadle reported a second series of 6 cases, one, a very severe case, showed great improvement during the first two weeks of iodin administration and then relapsed. This case illustrates very vividly the outcome which is so frequently seen today. Cheadle concluded his paper with the following state-

ment: "be the explanation of the beneficial effect of iodine what it may, the fact remains that the only decided improvement obtained by medical treatment in any of these cases followed the administration of iodine "

In 1911 Dr Ohlemann (13), a sufferer from Graves' disease, published an account of the treatment of his own case, which he states he cured by taking approximately 150 cc of tincture of iodine together with the occasional use of potassium iodide over a period of three years

Neisser (14) in 1920 pointed out that small doses of iodine are well borne by cases of Graves' disease and that such doses may notably improve their condition.

Loewy and Zondek (15) in 1921 reported a series of 12 cases in which they showed that the administration of potassium iodide in doses of a few milligrams daily would improve not only the nutrition but also the general subjective condition of the patients They reported three cases in which the respiratory exchange was reduced 19.9, 28.8, and 29.5 per cent respectively by the use of these small doses of potassium iodide

In 1924 Plummer and Boothby (16) reported a series of 400 cases of Graves' disease where large doses of Lugol's solution (10 to 15 mm once or twice daily) as a preoperative measure had been used and in which they also observed a lowering of the respiratory exchange just as Loewy and Zondek had previously found. This, however, was the first large series of cases in which respiratory exchange measurements had been made in connection with iodine administration. Subsequent reports of even larger series by Plummer and Boothby (17) showed that this initial fall in metabolism occurred in most of the cases Since then numerous reports by other observers have confirmed this temporary decrease in metabolism following iodine administration and its subsequent rise again in most of the cases where the use of these heroic doses of iodine is continued longer than two weeks The mechanism of this temporary fall in metabolism and consequent improvement of the disease is not clear. Plummer has supported the view that in Graves' disease the thyroid is producing an incomplete thyroxine of a highly toxic nature which the addition of iodine completes This is purely speculative without at present any founda-

tion in fact As we have repeatedly pointed out, this old view that the thyroid in Graves' disease is producing an abnormally toxic secretion was introduced by Moebius in 1886 and is open to many serious objections

In the first place the most serious cases of Graves' disease in general are those with the greatest degree of active thyroid hyperplasia and therefore associated with the lowest iodine store Secondly, it is this type of case which is most commonly benefited temporarily by iodine administration Thirdly, all the pharmacological effects of thyroid administration are proportional to its iodine content in whatever way this effect is tested whether by measurement of the respiratory exchange or the nitrogen excretion or by the Gudernatsch tadpole test Fourthly, feeding desiccated thyroid from cases of Graves' disease to cases of Graves' disease produces pharmacological effects in proportion to its iodine content We have fed as much as 11 grams of desiccated Graves' disease thyroid to severe cases of Graves' disease during eleven days, and have noted no alteration in their clinical condition whereas the feeding of 0.1 gram of standard desiccated thyroid may produce a very marked reaction In other words, if the Graves' disease thyroid contains no iodine it has no effect This is just the opposite of what should occur if the severe cases associated with marked hyperplasias were producing a more toxic secretion and we considered this experiment as additional proof that the thyroid in Graves' disease was not different from the thyroid of similar morphological and chemical constitution of other clinical associations

A much more rational view of the beneficial effects of iodine in cases of Graves' disease with marked hyperplasia is that the administration of large doses of iodine (especially inorganic) causes a rapid accumulation of colloid in the alveolar spaces just as the administration of iodine to cases with marked hyperplasia of other clinical associations in man, dogs, sheep, birds and fish The rapid distention of the alveoli with colloid brings about a *pressure retention* which temporarily blocks excretion until the thyroid cells have accommodated themselves to the increased tension Excretion is then reestablished and the metabolism begins to rise A similar effect of the rapid administration of iodine is regularly seen in simple goiter both in man and in animals This is well known and most physicians have seen cases



where in about seven days after beginning iodine treatment, the patient returns complaining that the thyroid is even larger than before, is firm to the touch and very painful (so-called iodine thyroiditis). Even with the continued use of iodine this effect generally wears off within two or three weeks. We have studied this phenomenon particularly in dogs where as early as the fourth day after the administration of large doses of tincture of iodine the gland, previously soft and spongy, because of the marked hyperplasia becomes very firm, and numerous histological examinations have shown that this firmness is due to the accumulation of colloid. When desiccated thyroid is administered this rapid accumulation of colloid and consequent firmness of the gland does not occur, because involution proceeds without the rapid formation and storage of iodine and colloid.

It has been asserted that Graves' disease associated with adenomata—the so-called “toxic adenoma”—is not even temporarily improved by iodine administration. This statement is in general true but there are numerous exceptions. The reason why iodine so seldom causes a lowering of metabolism in cases of Graves' disease associated with adenoma I believe is that the adenomata seldom react to iodine administration with involution and the storage of colloid and iodine. On the other hand, the cases of Graves' disease associated with adenomata that have reacted favorably to iodine administration are those cases in which a rapid accumulation of colloid with the storage of iodine occurs just as in the true hyperplasias. In an experimental study of the relation of iodine to the adenomata (18), we pointed out that certain adenomata would react to iodine with involution and storage just as ordinary thyroid hyperplasia, but that most of them had, more or less, lost this physiological attribute and that it was not possible to tell even from an histological examination which adenomata would and which would not react to iodine.

#### SUMMARY

Goiter is a compensatory or work hypertrophy of the thyroid in response to a real or a relative deficiency of iodine. The factors which may produce this deficiency of iodine may be grouped under three headings

Group 1 includes factors bringing about a real deficiency as occurs

in endemic goiter Water and food are the main normal sources of iodine and it has been abundantly shown that in goiter districts the iodine may be greatly reduced in both

Group 2 includes factors which divert an otherwise normal intake of iodine This is hypothetical at present, but it is conceivable that intestinal bacteria or parasites might prevent the absorption of an otherwise adequate intake

Group 3 includes factors which create a temporary or relative insufficiency, as for example diet, pregnancy, puberty, infections, Graves' disease, etc

The first group depends upon a definite, simply defined and easily understood factor—an actual deficiency in iodine, whereas the third group is more difficult to define, less understood, and by far the most important No animal with the ductless thyroid is free from the possible influence of one or another of the factors enumerated In planning and evaluating treatment, it is important to distinguish between groups 1 and 3 Emphasis on iodine starvation has been so prominent of late that the underlying cause of the iodine deficiency, whether real or relative, is often not taken into consideration For example, the thyroid enlargement of hereditary syphilis might not be noticeably influenced by iodine, whereas salvarsan might have a highly beneficial effect on both the syphilis and goiter

The greatest value of iodine in thyroid disease will always be in prevention Its value in treatment is limited and conditioned Simple goiter should be treated with desiccated thyroid combined with iodine This will relieve any functional insufficiency but as regards the deformity, much depends on the duration of the enlargement and the presence of complications like hemorrhage, cysts, calcification and adenomata The beneficial effects of iodine in the treatment of Graves' disease are limited, while its injurious effects are serious Its benefits are limited to relieving a real or relative functional insufficiency of the thyroid This iodine undoubtedly does, but until the cause of the thyroid stimulation in this disease can be relieved, no lasting benefit will occur merely from supplying the means with which the thyroid can manufacture more thyroxine more quickly Nevertheless, iodine should be given in all cases in doses not exceeding 1 mgm daily for a period of at least two months Iodine has generally

been used in much larger doses, and recently Plummer and Boothby have revived the temporary use of heroic doses particularly as a pre-operative measure. Unfortunately, the use of iodine in these large doses cannot be limited or controlled by the profession at large as Plummer recommends and much harm has and will continue to result from the use of these large doses.

The mechanism of the temporary beneficial effect of large doses of inorganic iodine in Graves' disease is not thoroughly understood. My own view is that iodine by causing a rapid accumulation of colloid in the alveolar spaces produces a *pressure retention* of the secretion until the cells accommodate themselves to function under the increased tension.

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# HYPOTENSION

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## HYPOTENSION

### INTRODUCTION

Low blood pressure is not a disease. It is, in many instances, a manifestation of a diseased bodily state. But it is established that distinct hypotension is in some instances compatible with perfect health. It is also true that many hypotensive subjects possess great bodily vigor. It therefore becomes a matter of interest to discuss the various types of low blood pressure, to determine their relation to various involved processes, and to establish, where possible, etiologic relations between the hypotension itself and the diseases of which it is a manifestation. Because of the complexity of the factors which influence and maintain blood pressure, this is a matter of some difficulty. Thus, in the condition or syndrome known as "essential hypotension," it has yet to be proved that the low blood pressure is the cause of all the symptoms. It may be that the low pressure, like the other signs and symptoms constituting the picture, is an effect of the underlying causal condition, rather than the true cause itself.

There is no single explanation which can account for all types of hypotension. It is not always pathological, and where it is a manifestation of disease, it may depend upon one of several underlying causes, or upon a combination of them.

Various methods for the determination of blood pressure are in use. For experimental work several exact methods are available, which are too complicated for ordinary clinical observation. Detailed discussion of such methods is unnecessary. For clinical study, the ordinary mercury manometer is sufficiently accurate, and is the most reliable machine for estimating pressures.

The auscultatory method of determination is the method of choice, although at times the combination of the auscultatory with the tactile method serves a useful purpose.

MacWilliam (1) has found disturbance of the auditory readings in a certain number of subjects as a result of compression producing

marked turgescence of forearm and hand The systolic pressure falls, and the diastolic pressure rises Such disturbances may occur while the actual blood pressure remains unchanged Under these circumstances the tactile method of estimation of the systolic index is of real value

In the vast majority of cases of clinical blood pressure estimation, however, the auscultatory method will be found to be perfectly reliable, and more accurate than the tactile method Diastolic pressure cannot be estimated by the tactile method at all Oscillometric methods are not in clinical use, to any great extent, nor are they needed

#### CLINICAL METHODS OF ESTIMATING BLOOD PRESSURE

There is no agreement among clinicians or physiologists as to what constitutes hypotension

Janeway (2) considered that, in adults, any systolic blood pressure below 100 mm constituted hypotension Oliver (3) on the other hand holds that pressure below 125 mm must be classed as hypotension

The majority of writers today however place the upper limit of the systolic pressure in hypotension at 110 mm in adults

Such variance in views would indicate that the normal limits of blood pressure in healthy individuals are not fixed

#### STUDIES IN NORMAL BLOOD PRESSURES

##### *Blood pressure in the newly born*

Rucker and Connell (4) made careful studies in fifty-two normal infants All figures were rechecked. They found the mean systolic blood pressure at birth to be 55 mm Hg, the mean diastolic blood pressure, 40 The systolic pressure increases with the age of the infant more rapidly than does the diastolic Toxic conditions of the mother seem to influence the blood pressure of the child, especially on the first day of life In general, the blood pressure varies directly with the total length of the child Neither sex nor color seemed to influence the blood pressure

Reis and Chaloupka (5) studied 100 cases of which 55 followed normal spontaneous deliveries in normal gravidæ The other cases

presented various complications during labor. Two premature infants and six sets of twins were included in the series. These authors found the mean systolic pressure during the first day of life in full term infants following normal spontaneous labor to be 43 mm Hg.

The blood pressure increases daily, until on the tenth day it reaches 78 mm. The greatest rise takes place during the first three days. The blood pressure varies directly with the weight. Sex, jaundice, pulse rate, temperature, and *caput succedaneum* without signs of compression, apparently have no influence on the blood pressure.

Infants delivered by abdominal Caesarean section have normal pressures.

Premature infants have low systolic pressures, corresponding to the length of gestation.

Twins have low pressures, proportional to the prematurity and the birth weight.

The greatest increase in blood pressure was found in infants after midplane forceps extraction and after versions. Lesser increases were shown after low forceps extractions, relatively dry labors, prolonged second stages, and in infants with large cephalic measurements. The increased blood pressures found seem to be due directly to increased trauma to the fetal head.

While giving definitely lower figures for the new born than those quoted above, Fabris (6) also finds that the systolic pressure stands in direct relation to the weight of the infant at birth, that it increases day by day. Pressure is lower in prematurely born infants. Sex and feeding methods do not influence the blood pressure.

### *Blood pressure in childhood*

It is generally agreed that pressure levels, both systolic and diastolic, are lower in childhood than in adult life. The difference is more marked with reference to the systolic which results in a diminished pulse pressure. Various authors have noted this fact. However, the increased pulse rate in children makes the product of pulse rate and pulse pressure approximate the volume flow for the adult.

Gniffith (7) says that blood pressure is low in children, exhibiting little if any increase up to puberty, when an abrupt rise occurs.

Judson and Nicholson (8) examining children from three to ten

years of age found average systolic blood pressure 92 to 100 mm., diastolic blood pressure 65 to 70 mm .

Faber and James (9) examined 1101 children, 651 boys, 450 girls. At ages 3 to 10 they found average systolic pressures of 90 to 100 mm. At ages 10 to 17 the systolic pressures showed no significant differences between the sexes at the ages studied. These authors point out the fact that hypotension in children, i e, pressures distinctly lower than the average, is rather common. Particular note is made of the fact that asthma in childhood is very commonly associated with hypotension.

Thomas (10) measured the blood pressure in 627 children from 7 to 14 years of age. Average systolic pressure in boys between ages of 7 and 11 was 98 mm, average diastolic 61 mm Hg. In girls of the same age the figures were 93 and 58 mm. respectively. In boys from 11 to 14 years, average systolic pressure averaged 107 mm, diastolic 71 mm. In girls of the same age the figures were 106 and 63 mm respectively. In tuberculous children, of the older age group, the figures were lower than in healthy children. This author finds that the variable amplitude of the blood pressure is from 5 to 10 mm greater in children than in adults.

In distinct contrast to the work of Judson and Nicholson and Faber and James on American boys, are the findings of Stocks and Karn (11) on British boys. The figures of Stocks and Karn are based on a study of pressures on 1323 British School boys, contrasted with those of 268 college students (both sexes) and forty adult workmen.

These authors found that up to 11 years of age the mean systolic pressure rises uniformly with age. (Most authors find a slow increase in childhood, in contradistinction to Griffith's statement.) After puberty the gradient of rise shows an acceleration. Taking the ages of 5 years, and 14 years, the American observers found average systolic pressures of 92 and 93 mm at 5 years, and 106 and 110 mm at 14 years. Stocks and Karn found a lower average at 5 years, 85 mm, and a higher level, 115 mm at 14 years. The rise as found by the British observers was nearly twice that as found by the American authors for approximately the same age period.

Stocks and Karn found that in their subjects, there is a rise, as

noted, after puberty, and that the pressure reaches a uniform level at about 18 years of age

In contrast to these carefully controlled studies, may be mentioned the work of Mouriquand and Barbier (12) who found mean systolic pressure averages as follows 3 to 5 years of age, 9 to 10 mm, 5 to 9 years, 10 to 11 mm, 9 to 14 years, 11 to 12 mm. These authors also state that diastolic pressures are not obtainable in very young children. These figures are so out of proportion to figures as obtained by all other observers that they may safely be disregarded as quite inaccurate. There is no difficulty in obtaining diastolic pressures in young children.

#### *Normal blood pressure in adult life*

In the last decade numerous statistical studies have been made by various observers, in an effort to obtain information as to average pressures in normal young adults, and with the idea of securing data concerning physiological variations in amplitude. As MacMillan justly puts it regarding such studies

While large numbers are of course necessary for statistical purposes, classification, etc., reliance on pressure measurement on a single occasion is apt to introduce sources of error, in view of the universally recognized tendency of single examinations to give results disturbed by temporary causes, nervous excitement, etc. More precise results, as regards the real pressure levels in individuals are obtained by a more intensive study of smaller numbers, by repeated examinations under carefully ascertained and controlled conditions.

In 1914 Melvin and Murray (13) made a series of studies on 59 medical students (sitting posture). The students were all over 20 years of age. The authors checked their figures by repeated observations. The systolic pressure average was 122 mm. In three cases the systolic pressure was up to 130 mm, in five it was 100 mm or below. The diastolic average was 65 mm in the majority of the cases, though in 12 the average was 55 mm.

Later observations have given distinctly higher figures for both systolic blood pressure and diastolic blood pressure, although several

observers, to be quoted presently, have specifically referred to a slight lowering of pressure in the early years of life

Alvarez (14) examined a group of 6000 men and 8934 women—freshmen entering the University of California. His observations were on systolic pressure made by the tactile method. He found that pressures of women are more uniform than those of men, and that they average 11 mm lower. In men, reclining, the pressures grouped mainly about 127 at age 16, 118 mm at age 30. In women (standing) average systolic at 16, 118 mm, 111 mm at 24, 117 at 40.

His studies showed that the average pressure (systolic) for both men and women drops gradually during the first years of adult life. In men the drop occurred from ages 17 to 21 and pressure then remained at about the same level to 50 years. In women the drop occurred during ages 17 to 25. There is a rise in women after the 25th year and a more marked rise after the 40th year. After 45 the average pressure is higher in women than in men. In a previous series Alvarez (15) and his associates had studied the systolic pressure in a group of 8737 University of California freshmen and in 1000 office patients. The mean pressures corresponded to those in his later series.

Alvarez found that hypertension, meaning systolic blood pressure over 120, was very common among younger men. About 45 per cent have pressures over 130 mm, and 22 per cent over 140 mm. Among women about 12 per cent had pressures over 130 and about 2 per cent over 140, and he believes that such hypertension cannot be ascribed regularly to infections or to the strenuous life. He believes that it is an inherited peculiarity, the appearance of which can be suppressed in women as long as the ovaries function. At any rate, such wide variations in perfectly healthy persons give food for thought. As one writer has sapiently put it, "One cannot forbear to inquire, in the face of all these figures, whether the criteria of hypertension, or at any rate the judgment as to its physiologic significance, are not too severe" (16).

Faber (17) examined 1000 Danish soldiers, ages 20 to 25, all in good health and found systolic pressures 110 to 130 mm in 80 per cent, and higher or lower, 84 to 156 mm, in 20 per cent. Such marked variations in the systolic pressures of healthy young men are striking. Explanations for such variations are to be discussed presently.

It would also appear that racial, environmental, and climatic conditions may change the normal average of blood pressure in young adults

Cadbury (18) made a study of the blood pressures in 774 young Chinese, all students in the Canton Christian College. These young men live in much better hygienic conditions than the average Chinese. They take part in athletic sports and eat a good quality of food. All students with evidence of cardiac or pulmonary disease were excluded from the series. For the age 20, 60 per cent of the readings of the systolic pressure (auscultatory method) were between 91 and 110 mm. Cadbury found that the systolic pressures of Cantonese and other Chinese young men averages 20 to 30 mm less than the normal for young men in Europe and America. He says that correspondingly low pressures have been observed among Bengali and Filipinos.

Conception and Bulatao (19) examined 717 subjects, average age 28, in the Philippines and found as averages in males systolic blood pressure 115 mm, diastolic blood pressure 79 mm, in females systolic blood pressure 116 mm and diastolic blood pressure 83 mm.

In Cadbury's studies the diastolic blood pressure was lower by 10 to 20 mm than the generally accepted averages for Europeans and Americans so that the pulse pressures showed little variation from the generally accepted norms. He comments on the fact that hypertension is very unusual in the Chinese, though chronic nephritis is exceedingly common. When found, hypertension is usually associated with valvular disease of the heart. Smaller stature and lighter weight of the Chinese as contrasted with average heights and weights of European and American youth, may account for some of the difference. Climatic variations and differences in diet may be factors but Cadbury is insistent that these young Chinese show *no* lack of vigor or dynamic force.

A more recent study by Kilbourn (20) is in accord with Cadbury's findings. Kilbourn studied the pressures of over 700 Szechwanese students. The mean systolic and diastolic pressures were lower than the standards for Anglo-Saxons of corresponding ages, but the pulse pressure was as high as that of the white races. The mean for 741 students was systolic blood pressure 111 mm, diastolic blood pressure



70, pulse pressure 40 Systolic and diastolic pressures of 9 Canadian and American boys (mean age 15) brought up in Szechwan, were markedly higher than those of the Chinese, but the pulse pressures were about the same Averages systolic blood pressure 120, diastolic blood pressure 80, pulse pressure 40 Within the limits of the investigation, the records showed no marked variation of pressures with age, though there was some variation according to body weight

#### HYPOTENSION IN APPARENTLY HEALTHY WHITES

In order to get data with reference to hypotension in apparently healthy persons, Friedlander wrote to the medical directors of the largest life insurance companies of America On the basis of their large experience, most of these men were convinced that hypotension in apparently healthy persons added to, rather than detracted from, their life expectancies

Fisher (21) in commenting on the published figures of the Northwestern Mutual Life Insurance Company writes "You will notice from the graphic description that our experience was estimated and was regarded as very favorable" In the pamphlet referred to there are the records of 3389 persons (ages 16 to 60) accepted for insurance by the Company, who had systolic pressures of 100 mm or less In this series there had been, up to the time of publication, 26 deaths, just 35 per cent of the expected mortality (American Men Table) The Northwestern Company's general mortality experience is about 80 per cent of that in the table

Muhlberg, medical director of the Union Central Life Insurance Company says in a personal letter

There appears to be no doubt of the fact that a low blood pressure past the age of 50, unassociated with any organic lesion to account for this low blood pressure, is the best criterion that we possess that the individual will live beyond his normal expectancy Just how low that blood pressure can fall without becoming actually pathologic is a matter that must, I imagine, depend on future clinical and statistical studies for solution

Symonds (22) reviewed a large group of 150,419 insurance risks He considers low pressures after 40 desirable He observed that the lighter built groups have lower blood pressure than heavier ones

In a study of arterial hypotension Barach (23) reported several group observations. Of 656 students at the Carnegie Institute of Technology, Pittsburg, 23 had systolic pressures between 100 and 110 mm Hg, and 7 had pressures between 90 and 110 mm. This gave a total of 30 hypotensives in 656 apparently normal young adults, an incidence of about 4.5 per cent. In a group of 31,596 recruits coming to Camp Sherman in the summer of 1918, 1315 were referred to the cardiovascular board for special study. In this series of 1315 recruits, which did not include cases of cardiovascular lesion or other organic disease, there were 73 cases of arterial hypotension, an incidence of 5.5 per cent.

In an examination of 1100 freshmen at the Carnegie Institute (Pittsburg) made in 1924, there were 24 cases of hypotension, (about 2.5 per cent).

Alvarez in the series already referred to found an incidence of 2.2 per cent of hypotensives, in apparently healthy males.

As a result of his studies, Barach draws certain conclusions as to the incidence of hypotension in persons apparently healthy. Discussion of his theory will follow later. At present it will suffice to call attention to the fact that statistical studies covering a good many thousands of apparently healthy young adults have disclosed the fact that arterial hypotension is quite common, being found in 2.5 to 3.5 per cent of all persons examined.

In the light of accumulated experience from diverse and fairly well controlled statistical studies, it appears justifiable to summarize the present viewpoints with reference to normal blood pressures somewhat as follows:

- 1 There is a slow but steady rise of blood pressure in childhood. The rising gradient undergoes a rather sharp acceleration at the pubertic period. The average adult level is attained, for both sexes, somewhere between the ages of 17 and 20.

- 2 There is some evidence of a slight lowering of pressure in the early years of adult life, perhaps slightly more marked in men than in women.

- 3 There is apparently little supporting evidence for the view, so commonly held, that there is an extensive rise in pressure in healthy persons as years go on. The pressure remains almost constant until

the age of 40, after which time the rise in pressure is more marked. And after 40, the figures for healthy women are somewhat higher than those for men. "But the rise, though quite a definite one, is more limited in amount than is commonly assumed, the total rise shown in the statistics due to the continued influences of age and increasing weight is on an average under 15 mm" (MacMillan)

4 While the averages, as found in studying large numbers of persons is fairly constant, it is undoubtedly true that great variations of pressures are found in certain percentage groups of apparently healthy persons. The causes for such aberrations from average normal standards are not clearly ascertained as yet. Various observers believe that heredity, producing fixed though aberrant types of cardiovascular or vasomotor mechanisms, or combinations of both, may be a factor.

5 Hypotension, systolic pressure of 110 mm or less, occurs rather commonly (approximately in 3 per cent of apparently normal healthy white adults), and probably more often than this in certain races (Chinese, Filipinos, etc.)

#### BLOOD PRESSURE DURING SLEEP

Landis (24) took tracings of blood pressure while the subject went to sleep, during a short nap, and during the period of awakening. Auscultatory readings of systolic and diastolic pressures were made. As the subject went to sleep, the pressure gradually dropped from approximately 110/74 to 98/68 mm. Certain of the curves assumed a definite pressure rhythm during this period. During sleep there appeared a more definite and a more pronounced pressure rhythm than when the subject was awake. Awakening as the result of sudden stimuli gave curves where the pressure rose sharply from a sleep level of 94 to 68 mm to 110 to 74 mm or higher.

Natural awakening other than that caused by sudden stimuli was marked by a more gradual return to the normal waking pressure. Body position, whether reclining or semi-erect, had little or no effect on the blood pressure during sleep. The general conclusion drawn was that change in circulation is resultant from, rather than causative of, sleep.

Blankenhorn and Campbell (25) also studied the effect of sleep on

blood pressure They used a specially devised apparatus for the automatic recording of several blood pressure tracings Their tracings conformed to the generally accepted standards of oscillatory measurements Hourly blood pressure determinations under basal conditions are presented the sleep being as natural as possible and the only definite variable in the experiment

Averages of twenty-five patients for 38 nights show the occurrence of the minimum systolic point (101 mm) at the fourth hour of sleep, a slight rise before waking, and an abrupt rise after waking to a point equal to the first hour of sleep The diastolic pressure shows a like though lesser fall The pulse rate shows a curve almost similar to the blood pressure The fall of the blood pressure is due mainly to the drop in pulse rate although it is probably somewhat influenced by the peripheral relaxation

The results of these two sets of observations run almost parallel, although Landis's figures for the drop during sleep showed lower levels Landis particularly stresses the point that change in position on going to sleep, or during sleep, caused very little difference in the curves He therefore believes that the drop in pressure results from sleep and that the sleep process is one of removal of superimposed neural control, and a return to a definite automaticity of function

Muller (26) found the systolic pressure to be down to 94 mm in men and 88 mm in women during sleep, after a small dose of veronal In persons with moderate day pressures Blume (27) records falls of 15 mm in men, and of 21 mm in women In subjects with high day pressures the falls were even greater

Katsch and Pandorf (28) also found a fall of the systolic pressure during sleep, the fall paralleling the depth of the sleep They assert that the diastolic pressure sinks little if at all, so that the pulse pressure is diminished MacMillan (29) has presented some hitherto unsuspected aspects of the subject of sleep and blood pressure He emphasizes the difference between sound dreamless sleep such as is known to be attended with lowering of blood pressure, and disturbed sleep with dreaming, which may be attended by remarkable elevations of blood pressure Of this latter type he records instances of rise of systolic pressure from 125 to 182 mm. or from 130 to 200 mm.

Diastolic pressure was raised from 75 to 105 mm. These changes were much greater than were induced in the same individuals by moderate exertion, walking, stairclimbing, cycling, straining abdominal efforts, etc. MacMillan's own comment on these suggestive findings (1) is rather striking

In view of the rapid development of such changes in sleep, especially in dreams of motor effort, nightmare, etc., it is evident that a formidable strain, harmless in the young and healthy person, may thus be thrown on the weak points of the circulatory system, whether these be cardiac with susceptibility to anginal attacks or to ventricular fibrillation with sudden death, or arterial with risk of hemorrhages cerebral (especially in the recumbent posture), gastro-intestinal or pulmonary. The conception of sleep as a period of quiescence and recuperation has thus to be qualified by the contingency of disturbed sleep with active calls on the nervous system, the heart and the blood vessels. The mechanism of the rise of pressure in disturbed sleep differs in some respects from that present in ordinary muscular exertion, since in the former the pumping action of working muscles, greatly augmenting the venous return to the heart, is absent. The above mentioned disturbances may occur during disturbed sleep when there is after awaking no recollection of definite dreaming.

These observations offer an explanation of the clinical fact, repeatedly attested, that patients with cardio-vascular disease awake in the mornings after fitful disturbed sleep, with exaggerations of their symptoms of subjective distress. The strain of marked rise in blood pressure where there is degenerative change in the cardio-vascular system is very definitely felt by these patients. And the apprehension with which these patients view the coming on of night, their oft repeated entreaty for something to give them sound dreamless sleep can be easily understood. Subjectively the disturbed sleep with its raised blood pressure causes much after discomfort. Objectively the hypertension, often repeated, becomes a source of real danger.

#### BLOOD PRESSURE AND MUSCULAR EXERCISE

It has been known for a long time that during brief or moderately prolonged periods of muscular exercise, such as stair climbing, hopping on one foot, bicycle riding, etc., the blood pressure is raised and the heart accelerated. These changes occur very promptly after the

exercise is started. The heart rate increases before the blood pressure rises. On the cessation of exercise the heart rate and pressure both fall. Under certain conditions of impaired myocardial efficiency the rise in pressure under exercise may be delayed, and at times when the myocardium is markedly impaired there may even be a fall in pressure during exercise. The simplest and best test of myocardial efficiency is thus the response of the cardiovascular system to exercise. As Hewlett (237) puts it, "The degree of circulatory failure in a given patient is estimated very largely by the amount of exercise that may be taken without inducing cardiac symptoms or by the relation that exists between the exercise and the severity of the symptoms induced." Various tests have been devised to study the effects of exercise on the cardiovascular system. Blood pressure, pulse pressure and heart rate readings have been taken before and after standard and graded exercise. Conclusions are drawn from the rapidity with which the figures after exercise return to the pre-exercise level. It is now generally agreed that no sweeping conclusions may safely be drawn as to the state of myocardial efficiency, based upon mathematical formulae as to time of return of pressure and heart rate figures after limited exercise. MacWilliam (238) has summarized existing views and present day knowledge of the effect of exercise on the cardiovascular system. He emphasizes the fact that measurements *during* the period of exertion constitute the only valid evidence as to the actual rise of blood pressure. The discordant results recorded by different observers dealing with exercises of different types and duration, or even with comparable exercises, are explained by the fact that the estimations are made *after* the end of the period of exertion. Working in MacWilliam's laboratory, Reid found that the rate, character and extent of the pressure changes after the end of exercise vary very much in different normal individuals and in the same individual under different conditions. It is also to be remembered that, in studies of arterial pressure response to exercise, the conditions of venous pressure have not been carefully estimated. MacWilliam also calls attention to the fact that the extent and course of the response of blood pressure to exercise varies a great deal in different types and degrees of muscular activity. That is, one must consider whether the effort made be strong or maximal, with fixation

of thoracic walls, or exercises of endurance such as walking, long distance running, cycling, execution of difficult though not necessarily strong movements, involving much mental concentration, or static contraction of muscles. It is also true that the cardiovascular responses to exercise in normal individuals vary considerably with reference to the state of muscular fitness and training of the persons tested. Gordon, Levine and Wilmaers (239) have recently made studies on a group of Marathon runners immediately after the conclusion of the race (25 miles). They found that the vital capacity of the lungs in Marathon runners was normal, indicating that prolonged vigorous training did not increase the breathing space of the lungs. There was a fall of 17 per cent in the vital capacity immediately following the race. This returned to normal in 24 hours. Immediately following the race there was a temporary decrease in heart size, determined roentgenographically. This returned to normal in about twenty-four hours. The systolic pressure immediately after the race was normal, while the diastolic was distinctly diminished. Shortly thereafter the *systolic* pressure fell, whereupon both pressures slowly rose to normal. Addis (240) studied the effect of exercise and of change of position in 300 normal persons. He found no constant relation between systolic and diastolic pressures after work. The degree of increase in pulse rate and pulse pressure varied with the amount of work and with the position of the body. In normal persons, tired by work, who were then required to change from the recumbent to the erect posture, there was an immediate decrease in the pulse rate-pulse pressure product. Such decrease in ratio associated with change in volume flow, coupled with recent evidence as to capillary contractibility, Addis thinks points to a failure of the circulation to meet the force of gravity. This failure is secondary to the failure of the central nervous system to produce with sufficient promptitude, an increased tone of the capillaries and venules which is necessary in order to prevent an accumulation of blood in the tissues when the erect posture is assumed. Where the cardiac weakness is the primary cause of circulatory failure, the pulse rate-pulse pressure curves show an unusual degree of uniformity in level before and after exercise. The absence of increase in pulse rate-pulse pressure product after exercise denotes a failure of that volume flow of blood with

which the normal heart meets the requirement of muscular exertion. Schneider and Truesdell (241) studied the effects of the exercise test on 2000 aviators. Pulse rate and blood pressure estimations were made with men recumbent, standing, after standard exercise and after two minutes rest. The correlations of recumbent to erect posture changes indicate a slight inverse ratio between pulse rate and systolic pressure changes. The authors feel that undue emphasis has probably been placed on these changes. The postural change is greater in the systolic than in the diastolic pressure. The correlations for exercise show a marked correspondence between systolic pressure and pulse pressure, also between diastolic pressure and pulse pressure. Stocks and Karn found that the change in blood pressure due to change from recumbent to erect posture varied very widely in the groups they studied. The average rise in systolic pressure was 3 mm, in diastolic pressure 10 mm, a fall of 7 mm in pulse pressure. The change was less marked in women than in men. They do not feel that it is possible to interpret these reactions as an index of physical fitness.

Discussing the effects of daily exercise on pulse rate and arterial pressure of men in the army, Scott (242) finds that regular training produces in men a decrease in the standing pulse rate, a lower diastolic pressure, and an increase in pulse pressure. The change in pressure from the recumbent to the erect posture tends to become less under training. In a group of men undergoing the same physical training the most "efficient" systolic pressure will be attained by some men with an increase, by others with a decrease. Physical efficiency is brought about largely by an increase in the tone of the splanchnic vasomotor mechanism. White and Moore (243) studied the response of arterial pressure, venous pressure, pulse rate and respiration rate, to a ten minute period of static exercise. The subjects were seated and held their legs horizontal. The authors found that the tendency of increased venous return during exercise, with increased venous pressure, is partially compensated by the venodilator mechanism, increased aspirating mechanism of the thorax, increased heart rate, and decreased diastolic pressure. There is a peripheral vascular mechanism which aids the return of blood to the heart. The effect of this mechanism is increased by exercise. Damez,



Dawson, Mathis and Murray (244) studied cardiovascular response to exercise in a group of 200 girls, in a summer camp in the Rocky Mountains. The high altitude of the camp (9000 feet), and the fact that mountaineering was the most important local activity made the observations of special interest. The plan of investigation was to use the Schneider and Crampton tests (see section on postural hypotension) and compare the reaction on girls grouped as "athletic" or "non-athletic." Among other things, the study showed that the athletic girl differed very little from the non-athletic so far as increase of pulse pressure on standing, rise in diastolic pressure on standing, rise in systolic and fall in diastolic pressure after exercise, and values of pulse product ( $PR \times PP$ ) whether lying, standing or after exercise. On the other hand the athletic girl's resting pulse is slower, her pulse pressure larger. On rising from recumbency her pulse quickens less, it is less after exercise, and it returns more promptly to normal.

Gillespie (261) investigated the relative influence of mental and muscular work on pulse rate and blood pressure. He found that mental work produces an increase in pulse rate and blood pressure, such increase being independent of emotional factors. This increase was not accounted for by movements of the articulatory muscles, nor by known muscle tensions. In combined mental and muscular work, the increases in pulse rate and blood pressure were greater as a rule than after mental or muscular work performed singly. In the case of women students the pulse rate increased proportionately twice as much as the blood pressure. In male students on the other hand, the proportionate increases in pulse rate and blood pressure were fairly similar.

Gillespie, Gibson and Murray (372) studied the effect of exercise on pulse rate and blood pressure. They found that the blood pressure rise is slower than the primary increase of pulse rate. The rise in blood pressure attains a maximum point early and then falls gradually and irregularly, in persons not fatigued by the exercise. The fall in pressure may be explained, they think, by the opening of numerous capillaries in working muscles. Krogh has called attention to careful quantitative measurements of the variations of numbers of open

capillaries in the same muscle at rest and at work (See section on Capillaries)

Wilson (373) studied the circulatory reactions to graduated exercise in normal children. His observations were made on 16 boys and 4 girls, varying in age from 6 to 13 years. Repeated records were made of pulse rate, systolic pressure and clinical symptoms following the termination of graded exercise. The exercise consisted in swinging dumbbells from the floor over head at a constant rate of two seconds for each swing. Observations were made in each case at two day intervals over a period of eight weeks. He found that the circulatory reactions to graduated exercise obtained in normal children were similar to those reported in adults. These reactions, immediately following exercise at two day intervals over a period of weeks were constant. The time required for the pulse rate to return to the pre-exercise level does not give much information as to the exercise tolerance of the child. After moderate exercise the systolic pressure rises. Where there is a delayed rise and a delayed peak of the systolic pressure, and a prolonged fall, associated with symptoms of fatigue and dyspnoea, it would appear that the exercise tolerance of the child has been reached or exceeded.

#### BLOOD PRESSURE AND BODY WEIGHT

Symonds (245) made a study of blood pressure of 150,419 men coming up for life insurance examinations. The men were grouped by ages and by build. Only the systolic pressure was studied. Age, weight and pressure were shown to increase together. Difference of 11 to 12 mm appeared between the youngest and oldest in each build group, and of 10 mm between the very light and the very heavy groups. Even at the ages of 60 and over the differences were much the same. There seemed to be a definite relation between blood pressure and body weight at all ages. The effects of obesity in increasing blood pressure are distinctly pronounced and have been emphasized by other observers also. Dublin, Fisk and Kopf (246) made reports of the principal findings in a group of 16,662 men, policy holders in the Metropolitan Life Insurance Company, examined by the Life Extension Institute. They found that there was

a higher percentage of hypertension cases (20 mm Hg or more above average for age) among overweights than in persons of normal weight. The findings with respect to low blood pressure indicated that overweight persons, high protein eaters, had relatively fewer individuals with low blood pressure than did the normal control groups. Dunham (247) made a series of 8645 reexaminations of commissioned and warrant officers of the United States Army, to study variations in blood pressure associated with variation in age and body weight. All men with any defect, except abnormal variation in body weight, were excluded from the series. The overweight persons averaged slight increases in pressure over the normals for the respective age groups. The underweight persons showed very little difference in blood pressure as compared to the normals.

#### THE FACTORS ENTERING INTO THE MAINTENANCE OF BLOOD PRESSURE

A discussion of hypotension must necessarily concern itself first with the consideration of those factors which maintain normal blood pressure. It is obvious that if one of these several prime factors is disordered, or if there is an imbalance of the normal interplay of these factors, that changes in blood pressure must occur. In the study of abnormal blood pressures, either high or low, it will become apparent that different variations of the normal factors, will produce manifold deviations from the normal. The evaluation of the rôles of these changes in the primary factors is at times exceedingly difficult. In some instances the relation of cause and effect is perfectly clear. In others, as in mixed forms, the explanation of the resulting change in blood pressure is not easy to find. Much has been done by the two methods of carefully controlled clinical study, and by experimental research, but it must be admitted that there are still many gaps in our knowledge. For some of the moot problems involved, no final answer is as yet available.

The factors which maintain blood pressure are these

- 1 The force of the cardiac contraction—the vis a-tergo
- 2 The condition of the vessel walls
- 3 The peripheral resistance to the blood stream, determined by the vasomotor system

- 4 The blood volume, and the physical state of the blood itself, its viscosity, etc

These factors are not of equal importance. It is obvious that if the myocardium becomes inefficient from any cause, so that it contracts feebly or inefficiently, the blood pressure will fall. This condition is common, and several types of hypotension of this sort will be cited and discussed.

The physical state of the conducting vascular system probably plays little rôle (30). To a certain limit, the blood vessels are capable of compensating by contraction for a loss of blood volume. Flaccid and toneless muscle fibers in blood vessel walls, such as might be found subsequent to the toxic influences of acute infection, might conceivably tend temporarily to lower blood pressure. Atheroma of the vessels certainly does not tend to lower blood pressure. On the other hand hypotension is not inconsistent with a marked degree of arteriosclerosis.

The third factor, that of peripheral resistance, is of very great importance. It is probably the most important single factor, both in the maintenance of normal pressure, and in the production of hypotension. Normally the arterioles, and the capillaries, are held in a state of tonic contraction by impulses delivered from the vasomotor centre. Peripheral constriction is thus subject to the ebb and flow of vasomotor impulses. The endocrine system works in conjunction with the vasomotor system, exerting either a pressor or depressor action on vasomotor function. Consequently morphologic—pathologic change in the ductless glands, or endocrine dysfunction play definite rôles in the production of hypotension, through the changes in peripheral resistance. It is thus evident that this factor of peripheral resistance presents a great many phases, many of them deviously interrelated. It is in the interpretation of hypotension associated with changed peripheral resistance that our greatest difficulties lie.

The fourth factor, change in the blood volume, is of very considerable importance in the production of certain types of acute hypotension. As has been mentioned, the blood vessels are capable (by contraction) of compensating only to a limited degree for loss of blood

volume When this limit has been reached, and there is no longer sufficient blood to fill the vessels, the pressure within them must necessarily diminish It is this factor which is of so much importance in the production of traumatic, post hemorrhagic, and shock hypotension It also occurs in conditions where there is great loss of body fluids, with consequent diminution of blood volume

Furthermore it is now known that relative diminution of blood volume is of great importance The measurement of systolic blood pressure is the determination of pressure exerted by a given volume of blood within the arterial system, extending from the left ventricle during systole to the smallest arterioles The researches of a group of observers including Dale, Laidlaw, Krogh and others have shown that the capillaries constitute "an actively contractile part of the vascular system having an intrinsic tone which can be modified either by nervous or chemical influences" (Dale) Only a small part of the total area of the capillary bed functions as a blood channel at any given moment Subject as the capillaries are to wide variations in volume during normal functioning of body activities, or as the result of pathologic dysfunction, it is apparent that the capillaries can produce very marked changes in relative blood volume By the induction of capillary stasis in one or another part or system of the body, the volume of circulating blood may be very profoundly reduced, with the consequent production of hypotension

Detailed discussion of the influences, chemical or nervous, producing such changes in the capillary beds will be had later The importance of this phase of the subject cannot be over emphasized

It is questionable whether the viscosity of the blood alone is a very important factor in the maintenance of blood pressure In general terms the viscosity of the blood stands in direct relation to the red cell count the viscosity is increased in polycythemia and decreased in anemia Increase in the viscosity of the blood increases the resistance to its passage through the vessels So that the hypotension found in certain of the anemias, the primary forms, and the more severe secondary forms, may be due in part to the diminished viscosity resulting from the greatly lowered red count Also, increased viscosity of the blood, in conjunction with other factors, does play a

rôle, as will be shown, in the production of secondary hypotension in traumatic shock.

#### TYPES OF HYPOTENSION

Low blood pressure may be either a temporary or a persistent phenomenon. Acute hypotension is part and parcel of traumatic, anaphylactic and anesthetic shock. It occurs as part of the picture in certain of the acute infectious diseases. It may be a result of certain drug intoxications. Persistent low blood pressure occurs in association with certain chronic infections, chronic diseases and, sometimes, in cachectic states. It also occurs in certain constitutional conditions such as infantilism, myasthenia gravis, status lymphaticus and myxedema. It is found in certain lesions of the circulatory system, particularly where there is myocardial degeneration. Both groups of hypotension cases, temporary and persistent, may at times be assignable to this cause. It is known that certain types of body habitus are associated with hypotension. There is the condition known as essential hypotension, marked by a fairly definite uniform syndrome, whose real nature is as yet not definitely understood. Chronic hypotension also occurs in certain conditions of disturbance of endocrine gland function, especially of the suprarenals, hypophysis, gonads, and thyroid.

In all of these forms of hypotension—and the enumeration above does not exhaust the list—one, two or all of the factors necessary for the maintenance of normal arterial pressure must be involved. But the correct evaluation of the rôle of these factors is, in many instances, a matter of extreme difficulty. For instance, even if the evidence is fairly strong that in a given case the peripheral resistance is diminished and the vasomotor center is at fault, there is still the question to be answered: what is the agent or the mechanism which provokes the disturbance of the nervous system? It must be admitted that for many of these hypotensive states we have as yet no adequate explanation. Recent studies in physiology, normal and pathologic, supported by clinical and experimental evidence have begun to shed some light on these very obscure factors. One difficulty in explaining certain forms of hypotension comes from the fact that the low blood

pressure is not due to a single factor at all. Thus it might be supposed that in certain diseases of the cardio-vascular system, such as myocardial degeneration, the hypotension would be directly attributable to the inefficient heart, with its enfeebled contraction. But investigation shows that even here the explanation is not so simple, that even here the hypotension depends upon an interrelation of the factors.

Added to this there is the further consideration that the amplitude of blood pressure figures consistent with perfect health is very great. The blood pressure varies in the same individual very markedly at different times, depending on differences in bodily activity, emotional stress, etc. Also, it has been pointed out that while statistical studies on a fairly extensive scale have been carried out to establish average norms, these very studies have shown that a very appreciable percentage of apparently healthy persons have a persistent hypotension.

#### TEMPORARY HYPOTENSION

##### *Anaphylactic shock*

In 1891, Hendenhain (31) showed that injections of peptone into the circulation caused persistent low blood pressure, with marked concentration of the blood. Later Pearce and Eisenbrey (32) (33) repeated these experiments, with others. They showed that, in the dog, anaphylactic shock is characterized by a low blood pressure resembling in many ways that of surgical shock. They concluded that anaphylactic shock and peptone intoxication are both accompanied by a condition of low blood pressure similar to that seen in shock and collapse. In both conditions there was a fall to a level of 20 to 30 mm Hg—prolonged in anaphylaxis, relatively short in peptone intoxication. The fall in blood pressure is due to dilatation (and congestion) of the large venous trunks of the splanchnic area, with coincident medullary anemia. The respiratory changes are in relation with this medullary anemia, only. The heart shows no initial changes. The greatly reduced volume of blood passing through the heart of course tends to further accentuate the drop in blood pressure. The authors concluded that the shock is due to peripheral vasomotor paralysis, not a muscular lesion. In explaining the underlying basis for anaphylactic shock, Hewlett (34) refers to the fact

that histamin produces physiological effects which resemble those of anaphylactic shock. He adds that there is considerable evidence for the belief that after the injection of a foreign protein, the antibodies formed in the body will react to this same protein, if it be subsequently injected, in such a way that an explosive digestion of protein occurs. The products of this protein digestion are believed to cause the phenomena of anaphylactic shock. In his study of low blood pressure associated with anaphylactic and peptone shock and experimental fat embolism, Simmonds (35) found that in peptone shock there is a marked, precipitate fall in arterial pressure, also a fall in venous pressure. In experimental fat embolism, the fall in blood pressure is always gradual and the venous pressure rises as the arterial falls.

Summed up, it would appear that anaphylactic shock is due to lack of vasomotor tone, resulting from splanchnic congestion and consequent disturbance of the blood volume.

#### *Traumatic shock*

For many years much study has been given to the question of traumatic shock. During the late war, English, French and American commissions, embracing in their personnels several highly trained observers, made a special study of the question. Facts of clinical observation and experimental evidence have been grouped, and so far as possible, correlated. Cannon, who had done much work on the subject before the war and who was a member of the American Shock Commission, has collected the material, resulting from clinical and experimental studies, into a monograph on the subject of traumatic shock (36). Cannon's conclusions as to the factors concerned in the production of traumatic shock are here quoted. No convincing evidence has been revealed

to show that either the heart muscle itself or the nervous agencies controlling the heart, exhibit any changes in shock which justify the conclusion that they are primary factors in lowering arterial pressure. The heart may indeed be injured, as may other organs, from a prolonged inadequate supply of blood, and when thus ill treated it may ultimately fail. Both clinical and experimental evidence, however, show that, when properly nourished, cardiac muscle is readily capable of carrying on its normal task [p 30]



Also, the conclusion is drawn from evidence presented, that ordinarily, in shock, exhaustion of the vasomotor center or even weakening of its tonic activity, is not *primarily* the cause of the low blood pressure. If the blood pressure is allowed to remain low for some time, bulbar centers, together with the heart and other organs, may have an insufficient supply of blood. Damage is certain to result if this condition persists, and in consequence there will be relaxation of motor tone [p 23]

Again

The theory of a secondary shock which has the strongest support both in clinical observations and in laboratory experiments is that of a toxic factor operating to cause an increased permeability of the capillary walls and a consequent reduction of blood volume by escape of plasma into the tissues. Thus the concentration of the corpuscles is also readily explained. It is recognized that after sufficient time has elapsed infection may occur and be of such character in itself as to induce a persistent low blood pressure. According to this theory there might be no essential difference between the effects of toxins given off by damaged tissue and of toxins resulting from the activity of bacteria [p 161]

The work of Dale and Laidlaw (37) and Dale and Richards (38) with reference to the drop in blood pressure following the injection of extremely minute amounts of histamin into animals is of particular significance with reference to traumatic shock hypotension.

The action of histamin may reasonably be regarded as typifying the action of a large class of protein derivatives, products of partial digestion, of bacterial action and of tissue extraction. Although proof is still lacking that a substance histamin-like in character, is actually given off into the blood stream when the tissues are severely damaged, the effects of local tissue injury (influencing the rest of the body solely through the circulation) and the effects induced by histamin are so similar that the supposition has a high degree of probability. In both conditions there is a fall of blood pressure. In both there is a reduction of blood volume. In both there is, at least in the early stages, a concentration of the blood. And in both, slight hemorrhage results in markedly increasing the shock like effect. It is a matter of considerable interest that proteolytic bacteria, such as those producing gas gangrene, induce in muscles chemical changes which, according to Zunz, are accompanied by the production of histamin.

Extracts of such muscles are highly toxic and rapidly depress the circulation. The association of "shock" with gas infection can thus be accounted for [Cannon, p 152]

Clinical evidence in support of the theory of toxemia as a cause of traumatic shock was accumulated largely by Quenu (39) who has also collected and summarized the studies of other French surgeons made during the war. The clinical evidence submitted shows that

1 Secondary shock does not appear immediately after the reception of wounds. So that it is not of the nature of a nervous effect. The state is commonly well established before infection, and therefore is not of bacterial origin.

2 It is characteristically observed in association with extensive damage of muscles or with multiple wounds scattered over the body. Several observers have described series of cases in which, without injury to bones, or to any vital structure or organ, there was extensive laceration of muscle accompanied by fatal shock in most instances.

3 Everything favoring absorption at the site of injury is favorable to the development of shock. Development of shock is most severe when the region of damage communicates with the exterior by only a small orifice.

4 Anything that delays or checks absorption from the injured region delays the development of shock, if there is sudden removal of the check, serious results follow. Cannon cites various illustrative cases. Thus in one case a tourniquet had been in place on the upper arm for an uncertain period. The wound in the wrist was so slight that the surgeon proceeded to clean it and take off the compression. The patient was in good condition before the tourniquet was removed. A short time thereafter, however, he went into profound shock and died.

5 Suppression of the injured region, if not too long delayed causes shock to disappear. If early amputation was had after lacerated wounds of the extremities, for instance, the results were very much better than if, for any reason, the operation had to be delayed. If time were allowed for disintegration of damaged tissue and absorption of toxic material, the resultant mortality rose very greatly.

In formulating and summarizing his theory of the nature of wound

shock Cannon lists the following factors These factors may be divided into initiating and sustaining factors, accounting respectively for primary and secondary wound shock Primary shock is most readily accounted for on the basis of some disturbance of the nervous system It is altogether probable that as a consequence of wounding, there is a reflex relaxation of blood vessels similar to that which occurs in fainting Thus there may be produced by a wound an effect similar in character to fainting or syncope, but persisting longer

The theory of secondary shock having the strongest support in clinical observation and laboratory experiment is that of a traumatic toxemia, with increased permeability of the capillary walls and a consequent reduction of blood volume It is quite possible that the toxic agent is either histamin or some histamin-like body

In addition to the toxic agents, hemorrhage, cold, exposure and anesthesia after hemorrhage may be factors in the production of the marked hypotension

When a low blood pressure is developing in consequence of the action of initiating factors, a critical level is reached below which the metabolism of the body becomes slower The body temperature becomes subnormal There is defective circulation with consequent anoxemia Damage to the nervous tissues is a direct result of this anoxemia In addition to this, however, there is relaxation of the capillaries and injury to the capillary endothelium A series of vicious circles would thus be set up

*a* The retarded flow in cooled capillaries would result in a lessened supply of heat to the regions of stasis This cooling would increase still further the viscosity of the blood, and the capillary blood flow would be still further retarded

*b* Increase in the number of corpuscles per cubic centimeter increases the viscosity Concentration of blood in some of the capillaries would result in greater functional resistance to the blood stream through them, with resultant increased capillary stasis

*c* As corpuscles accumulate in small veins and capillaries, transudation of plasma through capillary walls would be favored, with resultant diminution of plasma volume

*d* With capillary stasis, less blood is returned to the heart, the

arterial pressure therefore continues to fall. This diminution in driving force tends to increase the capillary stasis.

*e* As the blood pressure falls, the "head" normally in the arteries is largely lost. Circulation is not maintained equally through the body. The blood is forced through capillaries where resistance is relatively slighter. The blood flow in clogged capillaries, as those of extremities or intestines, would thus tend to be diminished, with resultant greater stasis.

*f* Reduction in oxygen supply to capillaries tends to dilate them. This increases capillary stasis and lessens the amount of blood being returned to the heart and kept in circulation.

### *Surgical shock*

As in the case of wound shock, surgical shock may be divided into primary and secondary manifestations. The onset of primary shock is probably most reasonably accounted for on the basis of some disturbance of the nervous system. Undue anxiety of the patient, dread of the operation, may thus be factors in the production of primary shock. Ordinarily this type of shock is not serious, but cases of fatal primary shock have been reported. Thus Isla (40) reported some unusual cases of primary surgical shock before the National Academy of Medicine of Spain. A man had been resident in hospital for fourteen years, his only trouble being a deformity of the left side of the nose. Isla suggested an autoplasmic operation. The patient finally agreed, but the next day he was dead. He had refused to eat or to speak the evening before operation. Necropsy showed no cause of death, which Isla felt was due to the patient's fear of losing his leisurely way of living.

A woman of middle age had a hydatid cyst of the liver. Operation was refused, but the patient agreed to have the fluid aspirated. The puncture was made, and the fluid had just begun to flow when the patient had a syncopal attack and died.

A man of thirty, of powerful build, asked to have his hydrocele tapped. The puncture was hardly over when the man dropped dead. Isla compares these cases of primary, fatal, wound shock, with several classical examples of death from nervous shock without operation.

Sophocles dropped dead when fellow citizens offered him a laurel wreath Diagoras expired suddenly when told that his three sons had won the Olympian games Dyonisius, the Syracuse tyrant, died suddenly on learning that he had been awarded the poetry prize in Athens

Cowell (41) also refers to the fact that in rare instances, severe primary surgical shock may develop as the result of sudden nerve stimulus Speaking generally, however, the term surgical shock relates to the manifestations of secondary shock accompanying or following surgical operations Among the factors tending to favor the occurrence of surgical shock may be mentioned hemorrhage, toxic agents from infection, loss of body fluids from various causes, chilling of the body, tissue trauma, handling of the abdominal viscera, and anesthesia itself Our knowledge of surgical shock has been derived from evidence accumulated by animal experimentation, and from clinical observation.

Epstein (42) believes that anesthesia itself plays an important rôle in the production of shock, because the anesthesia itself produces a very marked reduction in blood volume He made animal experiments on forty-one cats under anesthesia, some with, others without operative interference Susceptible animals show a prompt reduction of blood volume Experiments were done to show that this reduction in blood volume is not due to concentration of cellular content While increased salivation, mucous secretion and sweating may account, in part, for blood volume reduction in anesthesia, it seems probable that abstraction of fluid by the tissues from the blood plays the major part in this phenomenon Mobilization of lipoids and acidosis during anesthesia render the tissues more capable of absorbing fluid Epstein believes that the fact that the refractory animals show the slightest reaction would rather rule out the theory of acapnia as advanced by Henderson The reduction in blood volume in susceptible animals occurs promptly and is slightly increased by operation Mere prolongation of anesthesia does not materially affect the reaction Recovery from the anesthetic is attended by return of the blood volume to the normal

Discussing the causes of surgical shock, Clark (43) points out that during shock the arterioles are contracted tightly, that the heart

contracts strongly and is ordinarily capable of raising the blood pressure to normal, that the cause of the lowered blood pressure is the diminution of volume of blood in circulation. Insufficient blood returns to the heart to fill it and hence the normally contracting heart forwards but little blood into the circulation. The degree of diminution of blood volume is indicated by the work of Keith (44) who found that the plasma volume is reduced from 10 to 20 per cent in cases of mild shock and from 50 to 60 per cent in severe cases. That moderate hemorrhage alone does not in and of itself necessarily produce shock was shown by the studies of Robertson and Bock (45) who found that a reduction of the blood volume by 30 per cent may produce no disturbance of blood pressure, but that any further reduction causes a considerable drop in blood pressure. Experimental evidence has also been accumulated to show that the reduction in blood volume in shock is due to increased capillary permeability with consequent loss of fluid from the capillaries. Thus Cannon, Fraser and Hooper (46) found that in cases of shock the number of red corpuscles in the veins is nearly normal (4 to 6 million), while the capillary blood is greatly concentrated, having a red cell count of 6 to 8 million.

It is of course to be understood that in the production of surgical shock there may be the interplay of several causative factors. It has long been known that operations involving extensive injuries to tissues, especially to muscle, are particularly liable to produce shock. Bayless and Cannon (47) showed that crushing of the thigh muscles in cats produces a progressive fall in blood pressure with symptoms of shock. When however the blood vessels of the thigh were clamped, the shock effects did not supervene until the clamps were removed. McNee, Sladden and McCartney (48) found that application of a tourniquet centrally to the injured part was followed by rapid improvement.

That tissue trauma during operation may liberate toxic material which, in the presence of ether anesthesia, may produce shock has been suggested by Wallace (49). He points out that two operations involving approximately the same amount of cutting of large nerve trunks and nerve endings in the skin are amputation at the shoulder joint and at the hip joint. In the former operation where the limb is removed along tissue planes and where a relatively small muscular

mass is divided, shock is much less apt to occur than in the hip joint amputation where a very large muscular mass is traumatized

As to the nature of the toxic material produced by the injured tissues and causative of shock, there is as yet no definite knowledge. But, as Clark (43) points out, such effects can be paralleled by the injection of histamin. Dale (50) has noted that in the ether anesthetized animal, small doses of histamin caused very marked drops in blood pressure. In one experiment one mgm. of histamin per kilo given to an animal after two hours of ether anesthesia caused the blood pressure to fall from 160 to 33 mm Hg. When 2 mgm had been given the pressure fell to 26 mm Hg. Artificial respiration continued for an hour without ether did not bring about recovery. The blood became much concentrated hemoglobin before the injection of histamin was 75 per cent, after the histamin injection, 118 per cent. As Cannon puts it (51), "If histamin be taken as representative of toxic substances given off in consequence of bacterial action or of injury to tissues, it is evident that a general anesthetic such as ether may very greatly increase the sensitiveness of the organism to such substances."

In a study of the relation of the adrenals to experimentally produced hypotension Rich (52) finds that adrenalectomized animals, subjected to uniform intestinal manipulation before the blood pressure has begun to fall as a result of adrenalectomy, fall into shock exactly as do normal controls. The time required for the production of shock is the same in both series. It is therefore concluded that adrenal function is *not* a factor in the production of shock.

Animals that are kept *lightly* anesthetized with ether for an hour immediately before the abdomen is opened, become very resistant to the shock-producing effect of intestinal manipulation. Even when subjected to severe peritoneal trauma for a period of three hours, the blood pressure shows no tendency to fall. In contrast, if identical intestinal manipulation is begun more promptly after anesthetization the pressure invariably begins to decline. The fall is progressive and within two hours after opening the abdomen the animal is in complete shock. An hour's ether anesthesia preliminary to opening the abdomen has proved to be a striking protection against shock. But if the animal is anesthetized, permitted to come out and then re-anes-

thetized and intestinal manipulation begun, the protective effect of the preliminary etherization will have disappeared. These experiments are not in accord with generally accepted findings and need confirmation. The author found that ether has a distinct tendency to hasten the onset of shock once the blood pressure has begun to decline after the abdomen is opened. He also thinks that cardiac failure is not a factor in the production of shock, neither is failure of the vasomotor center a primary factor.

Muns (53) in a series of experiments on dogs found that ordinary third stage ether anesthesia prolonged more than one hour produced marked dilatation of the peripheral vessels, that there is direct relationship between vasomotor control and blood pressure and that the end result of ether depression is loss of vasomotor function and death.

On the clinical side Mann (54) has pointed out that in laparotomies entailing exposure and handling of the intestines, with exposure to the air, there occurs an immediate dilatation of all the arterioles in the exposed area. As a result of this dilatation of splanchnic arterioles, blood pressure falls. The splanchnic capillaries and veins are markedly distended, due to one or all of the following causes: local irritation of vasomotor tone, active dilatation, changes in abdominal pressure and venous obstruction. The process resembles the first stage of acute inflammation and does not appear to differ essentially from the phenomena as observed in classical experiments on the subject. Trauma to the viscera may thus produce shock, due to loss of circulatory fluid in the traumatized areas, mainly brought about by a local peripheral mechanism.

While admitting that free hemorrhage is a very common cause of shock, the author points out that all persons do not react in like manner to loss of blood and that the estimate of hemorrhage during operation is apt to be very inaccurate. Shock produced by excessive nerve irritation under anesthetic is probably much rarer than clinical reports would indicate. The adrenals are factors in some cases of shock, but it is very difficult to determine the relation of the adrenals, and other ductless glands, to shock. Deep etherization may produce most of the symptoms of shock. The depression following anesthesia is complicated by the hypotension, subnormal temperature and other changes.



McKesson has worked out a rule concerning the relation of blood pressure to operative procedure and to shock, basing his conclusion on a large series of clinical studies. Anesthetists have come to rely on this so-called McKesson law, which is as follows. A pulse rate of 100 and ascending, with progressively falling blood pressure reaching 80 systolic and a pulse pressure of 20 mm or less, if continued over thirty minutes, invariably ends in shock. McKesson has found that a considerable number of these patients who have had such readings will succumb within seventy-two hours unless treatment is promptly instituted, that is, as soon as the blood pressure falls and before the clinical evidence of shock is manifest. Discussing his own observations McKesson (55) said that the longer the low systolic pressure persists during operation, the less the likelihood of recovery of the patients. He stresses the fact that death in these cases frequently does not occur till the second or third day after operation. Such patients do not recover their cardiac tone. When the diastolic pressure is reduced but the systolic pressure is maintained somewhere near the normal, there is a cardiac compensation which saves the life of the patient. The heart moves a large enough volume of blood at each output to maintain circulation.

#### *Blood pressure and the anesthetic itself*

*General anesthesia* None of the general anesthetics in common use cause a maintained rise of blood pressure. Practically all of them cause a fall, if the administration be continued more than a few minutes. The amount of this fall varies very greatly with different anesthetics. Chloroform causes the earliest and most abrupt fall, ether has a similar, though less marked, action which occurs later, while nitrous oxide and oxygen causes very little drop in pressure unless the administration be very prolonged. The fall under chloroform sets in in about fifteen minutes, under ether in about twenty minutes. Gas-oxygen can be given for two hours without producing, in and of itself, any drop in pressure. After two hours under gas oxygen however a progressive drop occurs. But even this drop is different from that produced by ether because, as McKesson has pointed out, the fall stops as soon as the anesthetic is discontinued and within a few minutes the pressure rises to near the normal figure.

The drop in pressure under chloroform and ether anesthesia, apart from the effect produced by the operative procedure, is due, according to Clark, to depression of the vasomotor center and dilatation of the arterioles

It was shown during the war that anesthesia greatly favors the occurrence of shock. Comparison of anesthetics showed that chloroform has the greatest tendency to favor the production of shock, ether is less objectionable, and that nitrous-oxide-oxygen has less tendency than either of the others to aid in the induction of shock (Bazett (56)) Crile (57) showed the difference experimentally. He produced trauma by burning a cat's paw every half hour during anesthesia. Under ether the pressure fell 50 per cent in half an hour and fell to nearly zero in three hours. The same procedure under nitrous oxide-oxygen produced only a very slight fall in blood pressure.

Dale (58) found that the administration of chloroform greatly increases the toxic action of histamin in animals. With reference to ethylene gas, clinical evidence would indicate that in point of safety, as an anesthetic, it stands between ether and nitrous oxide. Special studies as to the effects of this anesthetic on blood pressure have not been made as yet.

*Local anesthesia* Andrejew (59) ascribes to the emotional condition, the drop in blood pressure often observed just before an operation. The lowering of pressure during an operation is due to operative trauma and length of operation. The more sensitive the tissues or organs the more the pressure will drop. Blood pressure may be low after operation, but unless a condition of shock is supervening it speedily returns to normal as a rule. His research on fifty-four women and thirty-four men during operations under local anesthesia demonstrated the value of watching the blood pressure during the operation. By this means it was found possible to detect the early signs of impending collapse or shock and thus, at times, ward it off. He suggests the advisability of supplementing the local anesthesia with a few whiffs of ether at the moment of greatest injury to the tissues, when it is not absolutely certain that all the centripetal nerve tracts have been blocked. Approximately similar conclusions were reached by Folstikov (60). He calls attention to the fact that before operations there may be a slight rise in blood pressure, due to psychic

influences At times during operations under local anesthesia the mental excitement continues, in which case the blood pressure may remain somewhat elevated during the operation.

Simon and Fontaine (61) found that in laparotomies under a local anesthetic the opening of the abdominal wall is accompanied by a transient hypertension, soon followed by a drop in blood pressure and pulse pressure General ether anesthesia, they think, causes the same effect but the consecutive decrease of the pressure is less pronounced These authors ascribe the decrease in pressure to the painful traction on nerves, which is therefore to be avoided as much as possible They found that blocking the gastric nerves in the rabbit prevented fluctuations in the blood pressure in operations on the stomach, and they therefore advise that in such operations on human beings an anesthetic should be injected into the mesentery in addition to the local parietal or the general anesthesia

*Spinal anesthesia* There is no doubt that under certain circumstances, spinal anesthesia lessens the added risk that general anesthesia would carry with it, where, for one of several reasons, the condition of the patient is very bad But there is also no doubt of the fact that in a considerable proportion of the cases where it is used, a very decided drop in blood pressure ensues So that the theory, formerly held, that spinal anesthesia prevents surgical shock is no longer altogether tenable It was found out during the war, as Robinson (62) points out, that operations under spinal anesthesia on soldiers who were suffering from shock, were exceedingly disappointing, and the procedure was abandoned In Casualty Clearing Stations where the proportion of operations done on patients in shock was naturally higher than at base hospitals or in England, spinal anesthesia had to be given up. Such patients were suffering from too much secondary shock already to be suitable for anesthesia by a method involving a further marked drop in blood pressure Also, in civil practice, the primary shock attending the induction of spinal anesthesia may be very considerable Here psychic factors doubtless play a great rôle

Still (63) believes that a fall in blood pressure accompanies each spinal anesthesia, and says that the drop may be so great as to be fatal In his experience the low point of the blood pressure is usually

reached ten minutes after the injection, after fifteen minutes one is working away from the danger point. He says that epinephrin given intravenously is of value in marked hypotension after spinal anesthesia. Other stimulants such as strychnin, caffeine, pituitary extract, given immediately after the induction of spinal anesthesia are of little value in warding off dangerous hypotension. He believes that a preliminary ether anesthesia of 10 minutes is the best prophylactic measure to ward off dangerous hypotension in spinal anesthesia.

Auer and Meltzer (64) found, as a result of experimental study in monkeys, that the intraspinal injection of epinephrin was of greater value in acute hypotensions, than where epinephrin was given in any other way.

### *Clinical studies of blood pressure during operations*

Marvin and Pastor (65) secured records of the blood pressure and took electrocardiograms at frequent intervals during the induction of anesthesia and during operation, and then made records of blood pressure and clinical course during ten or more days of convalescence. Observations were made on thirty patients. No selection of patients was made on the basis of age, sex, or cardiac condition. An effort was made to secure a wide variety of the more serious operative conditions. Preoperative pressures were taken at intervals for twenty-four hours. Preliminary readings were taken before operation and during the operations, pressure determinations were made at  $2\frac{1}{2}$ -minute intervals, electrocardiograms at 5-minute intervals. About 750 records were secured from the thirty patients studied, all of whom had major operations.

The authors found that blood pressure during operation may fluctuate within very wide limits, above and below its normal level, without other apparent change in the circulation or the general condition of the patient. The only change which seemed significant was the conspicuous and steady fall of blood pressure which accompanied the appearance of surgical shock. To the observers it appeared certain that the behavior of the blood pressure during operation afforded no indication of its subsequent behavior or of the clinical course of the patient. The majority of the patients in this series did not show the post operative fall reported by some observers and

assumed by many. Blood pressures during the first thirty hours after operation gave no information of value in estimating the likelihood of complications or the rapidity of convalescence. The electrocardiograms showed changes not found in preliminary tracings in about half the cases. These changes were chiefly premature beats, paroxysmal tachycardia and disturbances of the pacemaker. They seemed to be without clinical significance.

Malone (66) has studied blood pressure changes during cerebral decompressions. He finds that, clinically, blood pressure compensation following increased intracranial pressure is a valuable criterion of the degree of cerebral compression when the pupils react to light but of no service when they do not.

He does not decompress patients with falling blood pressure or with markedly subnormal pressure. He takes the low pressure to mean that the medullary centers are exhausted so that they can no longer compensate.

### *The treatment of wound and surgical shock*

*Wound shock* The war, which provided so much opportunity for the investigation of the causes and nature of wound shock, also gave great chance to devise the best methods of treatment for the condition.

The occurrence of primary shock of nervous origin was not frequent. Symptomatic treatment, rest and quiet are indicated along with measures, to be presently discussed, to increase the blood volume if the pressure be below the critical level. The most important thing is to prevent the occurrence of secondary shock if possible.

*Secondary wound shock* Keith (67) estimated the total volume of circulating blood by the vital red method, and the relative amounts of plasma and corpuscles by measurement of the hemoglobin or by means of the hematocrit. He has divided cases of secondary wound shock into three groups which vary from one another with regard to total volume of circulating blood and relative amounts of plasma and corpuscles in the blood. The differentiation he finds of great prognostic value on the one hand, and as a guide to treatment on the other. Group I constitutes the *compensated* cases. Here the blood volume is reduced to not more than 80 per cent of the normal. The plasma reduction is even less, the plasma being 85 to 90 per cent of

the 'normal' These cases have reacted like cases of hemorrhage there has been a migration of fluid from the tissues to the blood Such patients recover if kept warm and given fluids by rectum Group II constitutes the *partially compensated* cases The blood volume is reduced to 65 to 75 per cent, and the plasma is reduced in the same proportion Treatment by transfusion by one of several methods (see below) is necessary With proper technique, and if the transfusion be done early, the outlook is good Plasma volume must be measured within a few hours of the transfusion to see whether migration of fluid into the plasma has set in If not, a second transfusion is indicated In Group III, the *uncompensated group*, the blood volume is below 65 per cent and the blood is more concentrated than normal There is a relatively great decrease of plasma To be successful, treatment in such cases must be energetically pushed The outlook is bad because here the transfused fluid readily leaves the vessels causing pulmonary and tissue edema

As McLeod (68) points out, it is clear that fluid added by transfusion makes good the blood that is lost by stagnation, etc It thus tends to maintain a normal pressure in the circulation for a sufficient time to permit the organism to destroy the toxic bodies If the shock has persisted long enough to permit the nerve centers to be paralyzed, the injections are of no avail Many cases of shock have also had severe hemorrhage, and it becomes a question whether the shock really exists apart from the effect of hemorrhage Examination of blood and plasma volume aid in the diagnosis, as does the reaction to transfusion After hemorrhage alone there is great migration of plasma into the blood which thus becomes dilute Transfusion here has immediate beneficial effects In shock there is not only no migration of fluid into the blood, but actually the reverse is usually the case Consequently here transfusions cannot always succeed in re-establishing normal conditions

*Special indications in the treatment of wound shock* 1 Hemorrhage Further hemorrhage in cases of secondary shock may gravely imperil life There is thus the urgent need of preventing hemorrhage During the war it was found that the indiscriminate use of the tourniquet, the readiest method of controlling hemorrhage, was itself fraught with danger Cannon says that as a working rule the tourniquet

should be avoided altogether if possible. If one be absolutely required it should be placed as far from the trunk as conditions permit, and removed as soon as the vessels are tied or snapped. He also suggests (69) that if a limb has been so badly mangled that it cannot be saved, a tourniquet should be set close above the traumatized tissues and left in place until after the amputation. Thus, previous to operation, the body is protected against absorption of toxic material in the injured tissues.

2 Body warmth. It is of great importance to conserve the body heat left and if possible to restore that which has been lost. Suitable wrappings, the application of external heat as by hot water bottles, the use of hot drinks in suitable cases, the doing of dressings in warm places and the avoidance of unnecessary exposure of the body during necessary treatment may all be emphasized. During the war it was found that attention to the details of securing and maintaining body warmth was sufficient in many cases to bring low blood pressure back to normal.

3 Drug treatment. In the treatment of secondary shock, accumulated experience, gained by clinical and experimental study, goes to show the uselessness of many drugs formerly used. Even admitting that certain of these drugs, such as camphorated oil, injected into the circulation are cardiac stimulants, it is of course apparent that the heart itself is not primarily affected in shock. Such drugs as strychnin, alcohol, ether, ergot have all properly fallen into disrepute. It is the reduction in blood volume which is the great factor in the production of shock. It is for this reason that epinephrin and pituitary extract are of *no* value in the treatment of secondary shock. It is true that epinephrin constricts the arterioles so far as they are effectively innervated by the sympathetic. Pituitary extract acts by constriction of smooth muscle of the arterioles everywhere. It has a more lasting effect than adrenalin. As Cannon points out, arterial pressure may be temporarily raised by the intravenous exhibition of these drugs. But while the arterial pressure may be raised by these drugs, damming the blood in the arterial portion of the circulatory system obviously does *not* improve the volume flow in the capillaries. And Cannon adds that the desideratum in shock is a higher pressure which provides an increased nutritive flow through

the capillaries all over the body This cannot be brought about by any medication, but only by such measures as will definitely increase the blood volume, and thus help the volume flow through the capillaries

The best method to increase the blood volume is to increase the amount of circulating fluid Several ways of accomplishing this result have proved their value The simplest method of increasing a reduced blood volume is to give fluids by mouth When shock is well developed, however, vomiting is likely to occur, so that oral ingestion in such cases is not likely to be of much value Robertson and Bock (70) have showed that fluid administered by the alimentary tract, i e, both by mouth and by rectum, increased the blood volume markedly Thus, after hemorrhage, 250 cc of normal saline could be given every half hour in cases where there had been severe hemorrhage, so that in cases of non-urgent shock such simple procedures may be of great value Experimental study has failed to confirm completely the claim made by some observers, that normal salt solution given subcutaneously would increase blood volume None the less there is clinical testimony pointing to the probable value of subcutaneous saline injections in the prophylaxis and treatment of shock Gwathmey (71) says that in working with one surgeon, it has been his custom to use saline hypodermoclysis at the beginning of each operative procedure that is expected to last an hour or more He believes that this preliminary infusion enables the surgeon to obviate the occurrence of shock Ninety-five per cent of the patients so handled come off the operating table with a pulse of 72, normal respiration, and are in a most favorable condition for recovery Arbuthnot Lane advocates continuous saline infusion under the breasts, scapulae, or or elsewhere, in all operations where shock is anticipated As a prophylactic he considers the procedure of great value It is not suited for cases where severe shock is already present Such procedure probably has more of a place in the prevention of surgical shock than in the treatment of already present severe wound shock

4 Transfusion "Salt solutions fail to produce a permanent rise of blood pressure because they lack a colloidal material which, like the protein of the blood plasma, will not pass the capillary walls and which by its osmotic pressure prevents water from passing through"



[Cannon (72)] During the war Bayliss (73) advocated the use of 6 per cent solution of gum acacia. Such a solution in 0.9 per cent sodium chloride has the same viscosity as whole blood and the same osmotic pressure as blood plasma.

There has been much discussion and considerable diversity of opinion, both during and since the war, concerning the value of gum solution. British surgeons felt that when the solution was made from pure pearls of acacia, introduced warm and at a slow rate, the gum solution had no harmful effects. They felt that it had a valuable place in resuscitation, but that in order to have beneficial action it must be given early. Also, as has previously been noted, the injections must in some cases be repeated.

In 1919 Erlanger and Gasser (74) published the results of their experimental studies of shock treated with hypertonic gum solutions. They used solutions containing 25 per cent of gum acacia and 18 per cent of glucose. They found that such a solution acts beneficially in the treatment of shock, (*a*) by drawing fluid from the tissues to the blood stream, thus aiding in restoring blood volume, (*b*) by maintaining this increased volume through some property of the acacia, (*c*) by dilating arterioles through some specific action of the hypertonic crystalloid, (*d*) by increasing the energy of the heart beat in the same way, also through the direct action of glucose on the heart muscle, (*e*) by augmenting metabolism through increase in the supply of glucose to the organism.

Only small amounts of such a solution need to be given. 5 cc per kilo of body weight. On account of its great viscosity such a solution must be given very slowly.

In a paper published after the war, in 1922, Bayliss (75) discussed the advantages and disadvantages of the gum solutions. He emphasizes the fact that the sooner after injury the symptoms of shock are treated, the better the outlook. A preliminary injection of acacia is often of value even if subsequent transfusion of blood is used. There is no ground for the statement that acacia causes agglutination of corpuscles in man. The solution causes no interference with the return of fibrin to its normal value after hemorrhage. The retardation of clotting is inconsequential and is due to the dilution of the blood. The increased viscosity of the solution is a slight disadvan-

tage It is of course apparent that no artificial fluid can replace all of the blood There is some limit below which the supply of red corpuscles to the tissues would be inadequate for their oxygen supply Clinical and experimental data place this figure at about 50 per cent of the normal No advocate of acacia has suggested that it can replace more than half of the blood In answer to the statement that the osmotic pressure of even 25 per cent solution of acacia is not high enough to balance that of the corpuscles so that they swell and burst, it is pointed out that in practice either sodium chloride or glucose is added to give the requisite osmotic concentration So given, no hemolysis is produced If the 25 per cent solution is used it must be given very slowly in order to mix well with the blood The 6 per cent solution mixes very readily It is emphasized that acacia has no drug like action It is chemically inert like the serum proteins Its action is purely mechanical A second injection may be required at times The solutions must be made with great care, and the same care is necessary in acacia transfusion as with blood transfusion

5 Blood transfusion There is no question of the value of blood transfusion in shock Blood raises blood pressure, as does gum solution, in addition it gives to the patient a great increase of oxygen carriers, the red corpuscles Various observers have noted the fact that where the factor of hemorrhage enters largely into the production of shock, blood is distinctly preferable to any indifferent fluid And in the experience of men who had many opportunities for observation during the war, blood transfusion was found to be the most effective means of dealing with cases of persistent low blood pressure, whether due to hemorrhage alone, or shock To be of value in such cases the blood must be introduced early The injections must be made slowly In some cases they must be repeated During the war, blood transfusions certainly saved the lives of thousands of persons suffering from shock The drawback to the blood transfusion is that in military emergencies it is often impossible to make use of it as quickly as is necessary Such an objection naturally does not obtain in civil practice, in the treatment of surgical shock

*Treatment of surgical shock Prophylaxis* Frazer (76) urges that operation in a case showing persistent low blood pressure should be delayed, if possible, until means have been taken to raise the blood

pressure The operative procedure should be as short as is consistent with thoroughness It should be carried out with the least possible trauma, and every effort should be made to avoid unnecessary hemorrhage Chilling of the patient before, during, or after the operation is to be avoided Nitrous oxide-oxygen should be the anesthetic of choice Transfusion of blood or of gum solution must be employed if the pressure remains near the danger limit

Coburn (77) is an earnest advocate of gum-glucose solutions in operative cases with low blood pressure He emphasizes the importance of maintaining a good blood pressure during the first operative period

Cowell (41) says that the bulk of cases of surgical shock correspond to wound shock The pressure falls toward the end of the operation or even after the patient has returned to bed The anesthetic itself, the amount of hemorrhage, the amount of tissue trauma are all factors in the production of secondary surgical shock He prefers gas oxygen as the anesthetic either alone or combined with regional anesthesia He advocates the use of gum solutions during the operation if the pressure begins to fall sharply and stresses the fact that the ordinarily used stimulants are of no value

With reference to regional anesthesia Harke (78) notes that in splanchnic anesthesia there is apt to be marked hypotension assumed by many to be due to the novocain This is apparently successfully combated by the injection of pituitary extract In 24 of 28 cases where splanchnic anesthesia was used the sudden drop in blood pressure was avoided by the preliminary injection of pituitary extract

Fisher and Mensing (79) report five cases of early surgical shock where the intravenous injection of glucose, combined with the subcutaneous administration of insulin, caused a rapid disappearance of shock symptoms

Geist and Goldberger (80) felt that preoperative digitalization reduced post operative shock On the other hand, Marvin, Pastor and Carmichael (81) made a careful series of studies on a group of patients with a wide variety of ages and operations They found no convincing evidence that the preoperative administration of digitalis exerts a favorable influence on the blood pressure or the incidence of postoperative complications As has been pointed out, surgical

shock is not primarily a cardiac affair, so that this conclusion would seem to be in accord with accepted clinical and experimental evidence

Naffziger (82) stresses the point that in operations on patients with arteriosclerosis, special attention should be given to the avoidance of sudden drops in blood pressure. This holds good particularly in the case of cardiac decompensation. In all cases with cardiovascular lesions every effort must be made during operations to prevent drops in blood pressure. Special attention should therefore be paid to the blood pressure during operation. The loss of body fluids is to be prevented, so far as possible. When such loss has occurred, the replacement by fluids per rectum, under the skin or intravenously is advocated. The position of the patient on the table merits special attention in these cases. Cerebral anemia is lessened by the Trendelenburg position. But the restoration of the patient to the horizontal or head up position is to be accomplished slowly and with careful blood pressure observations at this time.

The modern treatment of surgical shock follows the accepted standards for treatment of wound shock as detailed above.

#### HYPOTENSION IN ACUTE INFECTIOUS DISEASES

Most of the acute infectious fevers are accompanied by a fall in blood pressure, though the drop is more marked in some than in others. In general terms the extent of the fall varies directly with the degree of fever. There are however definite exceptions to this rule. The type of infection, the general condition of the patient antecedent to the infection, and the fact that in some instances the pressure is influenced more by the toxemia than by the pyrexia, all militate against the working of the rule.

During the height of fever, blood flow, especially in the capillaries, is slower than in health. Such relative capillary stasis would be a factor in the production of febrile hypotension. Newburgh and Laurence (83) showed that in lower animals, experimentally induced hyperthermia of degrees not greater than those encountered in infections, is sufficient to produce marked hypotension. Clinically it may be said that the increased body temperature in infection is one factor in the hypotension which occurs. The weakened heart action, due to the cloudy swelling or degeneration of the heart muscle in

certain of the acute infections is another factor, the *vis a tergo* is lessened. In convalescence from prolonged fevers there is often a loss of splanchnic tone, due in part to nervous influence (toxemia) in part to weakened arterial musculature. This tends to lower blood pressure still further. When the patient assumes the erect posture, the decreased cerebral supply must be compensated for by increased pulse rate, and this throws an added strain on the heart.

It is thus apparent that various factors enter into the production of hypotension in the acute infectious diseases. Norris (84) rightly stresses the fact that the actual figures of blood pressure, are not of as much value as the course of the pressure curve, upward or downward. Lability of pressure, with marked changes in pulse pressure is of importance.

### *Typhoid fever*

Apart from certain complications, and at the onset of a relapse when a slight but transient rise in pressure is often noted, the course of the blood pressure in typhoid is progressively downward. Of 58 cases studied by Rolleston (85) 54 (93.8 per cent) showed subnormal readings, the few exceptions being in children. Knox (86) also notes that in the typhoid of children there is very little variation in blood pressure. Rolleston makes the rather extreme statement that the degree and duration of the fall in pressure in typhoid are more marked than in any other acute infection. He believes that the hypotension is in direct relation to the severity of the attack. The systolic pressure is nearly always below 100 at some time during the attack, and in nearly half the cases studied by Rolleston normal pressure for age was never regained while patients were in hospital. With the advent of hemorrhage the pressure usually drops very sharply. Such a drop in pressure is to be explained by the diminution of blood volume. A sudden rise in blood pressure in typhoid is found when perforation has occurred. Crile (87) believed that such a rise was of importance as a diagnostic sign of perforation, reporting that it often occurred very early, due to constriction of the splanchnic vessels. Other authors have reported rises of as much as 50 mm after perforation but, as Miller (88) points out, the finding is too inconstant to be of diagnostic value. In association with other findings it may have confirma-

tory value In order that blood pressure changes in typhoid may have diagnostic value, daily readings must be made during the course of the disease Rolleston found transient rises in pressure due to pleurisy and cholecystitis complicating typhoid

Involvement of the myocardium is of course extremely common in typhoid The cardiac factor is thus of prime importance in the causation of the hypotension The vasomotor factor doubtless also plays a rôle, i e., there is toxic vasomotor depression

### *Pneumonia*

Hypotension is found, more or less marked, in the majority of cases of pneumonia Cole (89) calls attention to the extensive studies that have been made of the blood pressure in pneumonia, and to the lack of uniformity of findings of various observers He does not believe that the degree of hypotension is an index of the severity of the disease and he notes the fact that, at times, desperately ill patients may have high systolic pressures up to the period immediately preceding exitus

The hypotension in pneumonia is probably not due to the mechanical embarrassment of the right heart offered by the exudate in the affected lung The hypotension is due in great measure to the toxemia and its effect upon the vasomotor centers Attention has repeatedly been called to the fact that death in pneumonia is frequently attended by the signs and symptoms of surgical shock Clinicians have long been accustomed to rate the degree of toxicity by the severity of these "shock" symptoms during life This has been formulated into a prognostic rule by Gibson in his ratio of pulse rate and blood pressure Arterial blood pressure, expressed in millimeters of mercury, falling below the cardiac rate, expressed in beats per minute is of grave prognostic import

It is undoubtedly true that the condition of the heart muscle itself is a factor in the production of hypotension in some cases of pneumonia The recognition of this cardiac factor has led to the wide spread practice of routine digitalization in the treatment of pneumonia The beneficial effect of cardiac stimulation for the heart in pneumonia, and the effect on the blood pressure are illustrated by the following figures from a case on Friedlander's Service, Cincinnati General Hospital

J C C, male, colored, aged 28, admitted January 5, 1926 Lobar pneumonia right middle and right lower lobes Marked myocardial weakness. Patient extremely toxic

Blood pressure on admission 78/44 Ouabain gr  $\frac{1}{250}$  given intravenously (There had been no previous digitalization) Twelve hours later blood pressure 90/60 Ouabain repeated, twenty-four hours after first dose Twelve hours later blood pressure 112/72, and maintained thereafter

The hypotension in pneumonia is thus probably due to a cardiac factor, a toxic vasomotor depression factor, or a combination of both of these

### *Influenza*

Hypotension is the rule during the acute stage of influenza During the last pandemic it was generally noted that the asthenia reached very extreme degrees This was particularly true in places where, owing to the segregation of large numbers of persons as in army camps, the virulence of the epidemic was especially great Thus at Camp Sherman, Ohio, there were 19,000 cases of influenza within two weeks, with a mortality of 1054 men The present writer, who had occasion to observe this epidemic at close range, was especially struck with the intense asthenia which formed part of the syndrome And this held good not only for the fatal cases, but was generally true for the milder cases which ran their course without particularly severe complications It was also noted that the hypotension and asthenia persisted for a long time after all the acute manifestations of the disease had passed The factors at work in the production of this influenzal asthenia are (a) the cardiac factor, (b) the vasomotor factor and (c) changes in blood volume Underhill and Ringer (301) call attention to the similarity of influenza and acute phosgene poisoning, from the point of view of pathology Influenza and gas poisoning produce strikingly similar effects on the respiratory tract In both of them, pulmonary edema is a prominent feature In both, the blood becomes markedly concentrated so that there is a marked reduction in blood volume This constitutes a factor of the greatest importance in determining a fatal outcome The degree of shock and consequent hypotension is measurable by the degree of change in blood

volume Cumston (302) calls particular attention to the marked asthenia and hypotension in influenza. He finds that hearts, already the seats of lesions, particularly myocardial lesions, more readily become the prey of the influenzal virus than do normal hearts. He notes that cardiac changes may appear suddenly. The onset may be very rapid, with marked precordial distress, asthenia, hypotension, cyanosis, alidity and intense dyspnoea. If these cases recover, the myocardial lesions may persist for a long time in a very considerable proportion of the cases. The frequency of such myocardial degenerative changes after influenza has been noted by various writers. Gallop rhythm, with marked hypotension and signs of cardiac distress, on even slight effort, are commonly found. In a smaller proportion of the cases influenzal bradycardia, persisting for very long periods of time, has been found. Cumston finds that many of these cases show persistent hypotension. Blumgarten and Voss (303) list as causes of death in influenza (a) acute myocardial insufficiency, (b) acute pulmonary edema, (c) hemolysis—cyanosis which gradually grows more marked till death ensues.

Minet and LeGrand (304) discuss the various sets of symptoms that may be presented according to whether the myocardial factor, the vasomotor factor, or the endocrine factor is the cause of the asthenia. They too emphasize the fact that the hypotension after influenza, persists for a very long time. A very interesting survey of a cross section of a civilian population was made after the influenza epidemic in Cincinnati. Mason (305) reports the results of this survey which was made by a group of health agencies. 7058 persons having had influenza were examined about a year after the subsidence of the epidemic. Of these 828 (10.3 per cent) still showed marked hypotension, 643 (9.1 per cent) showed evidences of myocardial degeneration. According to their statements the persons in both of these groups had been in good health before the epidemic.

It is well to remember also that the lack of vasomotor tone after influenza is very marked and very persistent even in cases without cardiac involvement. The explanation of many cases of persistent asthenia and hypotension seen during the past few years, since the influenza pandemic, may be that they originated in acute influenzal attacks.



*Diphtheria*

A marked fall in blood pressure occurs in the more severe cases Harding (90) as the result of her study, finds that in such cases there is a marked reduction of blood volume, and a markedly uneven distribution of the blood. This would agree with the findings of other observers that in the early stages at least the hypotension was vasomotor in origin. Stejskall (91) Enriquez and Holly (92) Passler and Rolly (93) and Gottlieb (94) all showed in their earlier studies that the hypotension is certainly not due exclusively to vasomotor depression, in that the myocardium itself is directly involved. Porter and Pratt (95) as the result of experimental work on animals (done in 1914) found that even in the late stages of lethal diphtheria, the vasomotor system still responds to both pressor and depressor stimuli, showing that death is not due primarily to vasomotor paralysis. MacCallum (96) at about the same time submitted evidence to show that death in the height of an attack of diphtheria is not *exclusively* the result of direct injury to the heart.

It is thus apparent that both cardiac and vasomotor factors enter into the production of the hypotension of diphtheria. The importance of the *early* administration of antitoxin is thus easily understood. The most marked drops in pressure occur in those cases in which antitoxin treatment has been delayed. Early exhibition of antitoxin in full doses greatly lessens the chance of permanent myocardial damage. Progressive drops in pressure are of bad prognostic import.

Persistent tachycardia is also of bad prognostic import. Smith (97) as the result of 242 cardioclinical and electrocardiographic studies of the heart in diphtheria found that 65 per cent of arrhythmias persisting to convalescence are either sinus arrhythmias or sinoauricular block. About 20 per cent are due to premature contractions and the remaining 15 per cent are due to heart block. The use of digitalis in diphtheritic arrhythmias, as a routine treatment, he strongly condemns. Place, as the result of his clinical studies is in accord with this dictum. Benefits accrue from lessening the work put upon the heart rather than from attempting to raise the heart's capacity to do work. He also emphasizes the fact that cardiac injury occurs most often in the neglected cases and strongly urges the early administration of antitoxin.

Rolleston (98) finds that the blood pressure tends to be subnormal in diphtheria, the extent of the depression bearing direct relation, as a rule, to the severity of the angina. In the great majority of the cases, the lowest readings are found in the second week of the disease, normal tension being recovered by the seventh week. In laryngeal cases disproportionately high readings for the age of the patient are obtained. Relief of the obstruction is usually followed by prompt fall. The pressure tends to fall with the onset of paralysis. In Rolleston's opinion routine readings of the pressure are not of much practical value.

Munk (99) believes that epinephrin is of much value in increasing the blood pressure due to circulatory failure in diphtheria.

### *Scarlet fever*

There have been comparatively few studies of the blood pressure in scarlet fever. Most writers feel that the variations in pressure here are not remarkable, and not uniform. Doria (100) finds hypotension in scarlet fever similar to that in other infectious diseases. He thinks that it is due to vasodilation and to weakness of the left ventricle, i.e., a combination of the vasomotor and cardiac factors. He makes the point that albuminuria with low pressure is usually not followed by nephritis. If this be true, it is a diagnostic sign of value, but this observation needs confirmation.

The frequent association of scarlet fever and diphtheria is to be remembered. McCrae's statement is that "scarlet fever and diphtheria are deadly diseases and the combination is more powerful than the added strength of the two." In such a combination the degree of toxicity is usually high, and in consequence such cases are apt to show a marked hypotension.

### *Cholera*

In the algid stage the systolic blood pressure falls markedly. Pressures as low as 70 mm Hg are not uncommon. The diastolic pressure does not fall to the same degree so that there is a marked diminution in pulse pressure. The very low pressures are due to the loss of plasma from the circulatory blood. The polycythemia that follows causes a marked increase in the viscosity of the blood, and this in-

creased viscosity is further heightened by the low body temperature. Here then, changes in blood volume are the causative factor in the hypotension. The use of intravenous saline transfusions, whose value has been repeatedly attested clinically, is to be recommended because the restoration of blood volume tends to overcome the hypotension. Rogers (101) advocated the use of hypertonic salt solution with epinephrin. Experiences at the San Lazaro Hospital in Manila showed that normal saline solution gave just as good results (102). Up to the present time there have been no reports published of any serum in the treatment of cholera that will give as satisfactory results as the intravenous injection of salt solution.

### *Malaria*

Marked hypotension has been found in many of the severer cases of malaria, though this finding is not always present. It is of course much more common in chronic malarial cachexia. Paiseau and Lemaire (103) have reported very low blood pressure in pernicious malaria associated with cramps and white dermatographia (Sergeant's line). The autopsy in these cases revealed hemorrhagic and necrotic lesions of the adrenals. Fulchiero (104) reported three cases, in all of which the typical Addison's syndrome was found. Under treatment for malaria, and with the exhibition of epinephrin, all of the Addison symptoms subsided. The pigmentation however remained practically unmodified.

As a result of their clinical and experimental studies, Bass and Johns (105) believe that the plasmodia lodge in the capillaries, especially where the circulation is weakest. Thus a very heavy infection may result in plugging brain capillaries to such an extent as to produce coma and cerebral malaria. These authors found that the size of the capillaries and the blood pressure have an important influence on the stage at which malarial plasmodia recede from the peripheral circulation into the capillaries, to undergo segmentation, or to invade new cells. They may thus be factors in the production of cerebral blocking. Thus, after reaching a certain size the plasmodium reaches and lodges in the capillaries. In this situation the inoculation of new corpuscles normally takes place. The debris and pigment resulting from their destruction might thus plug the cerebral capillaries and produce cerebral malaria.

*Epidemic cerebrospinal meningitis*

In contradistinction to most authors who find hypertension associated with epidemic meningitis, J D Rolleston (106) says that in severe cases, especially in adults, the blood pressure may be very low. He finds that during the course of the disease, the blood pressure may show marked fluctuation. In contrast to other authors also, Rolleston finds that lumbar puncture with removal of fluid is usually followed by a slight fall. He also finds that the intrathecal injections of fluid (e g, serum) usually causes a marked fall, this fall being in direct ratio to the amount of fluid introduced. Friedlander's experience (107) with the disease in army camps during the war does not coincide with this view.

*Typhus fever*

The pressures in typhus are usually extremely low both systolic and diastolic. Palfrey and Wolbach (108) emphasize the fact that records of blood pressure do not show obvious relation to the outcome of the disease. The heart in typhus does not show as marked myocardial change as is the case in typhoid. The hypotension here is therefore probably not cardiac in origin. In all probability toxic vasomotor depression is the basis of the hypotension.

*Trichinosis*

Cheney (109) reports a case of sporadic trichinosis with extreme hypotension. A male adult was brought to hospital complaining of general weakness. On the second day, with a temperature slightly above 100°F, the blood pressure fell to 44/18, checked by three observers with different instruments. One cubic centimeter of epinephrin was given subcutaneously and the blood pressure rose to 110/48, gradually falling to a constant level of 70/42 after six hours. It gradually rose during the remainder of the patient's four weeks stay in hospital reaching the figures of 102/64 at discharge.

Hypotension in trichinosis has recently been described by Gruber (110). He agrees with the findings of Maase and Zondek, who find that marked hypotension occurs in severe cases of trichinosis very commonly. American writers have hitherto not called attention to

this phenomenon Gruber finds that severe cases are usually accompanied by marked degeneration of the heart muscle Glaeser and Flury have been able to demonstrate in vitro and experimentally the presence of a toxin extracted from the trichina itself Thus the cardiac degeneration is explained The hypotension in trichinosis is therefore in all probability of toxic myocardial origin

*Tsutsugamuchi disease (Japanese flood fever)*

Kawamura (111) has recently published a monograph on tsutsugamuchi disease, an infectious disease caused by the bite of a sand louse (akamushi), and occurring endemically along certain river basins in the Niigata prefecture of Japan The clinical picture to some extent resembles that of typhoid, with the addition of a generalized adenopathy Hypotension is the rule in the disease The systolic pressure falls below 100 mm and at the end of the fastigium or the beginning of defervescence lies between 90 and 100 mm, becoming normal during convalescence Blood viscosity and coagulability are both decreased during the febrile period The heart, in fatal cases coming to autopsy always shows a marked cloudy swelling The hypotension is doubtless due to myocardial weakness, the result of the toxemia induced by the bite of the akamushi

HYPOTENSION IN CHRONIC DISEASES

*Tuberculosis*

The relation of low blood pressure to pulmonary tuberculosis has been made the subject of study at various times In the advanced stage of the disease, with pronounced toxemia, marked hypotension is the rule In the incipient stage however, there is no constant hypotension Janeway (112) showed that there were no marked differences in pressure between a series of non-tuberculous and incipient tuberculous patients These findings were confirmed by Shalet (113) in a study of one thousand cases Landis (114) says that the blood pressure is low during the active stage of the disease As the lung heals and the symptoms disappear, the blood pressure rises to the normal level He stresses the point that in cases of masked or occult tuberculosis, a low systolic pressure, and a marked drop in pulse

pressure on assuming the erect position, is of great diagnostic significance. There is still, however, some diversity of opinion with reference to the diagnostic and prognostic value of the study of blood pressure in tuberculosis. Marfan and Vanmeuwenhuyse (115) in a study of seven hundred cases found hypotension, its degree standing in direct relation to the severity of the process. They do not regard hypotension as excluding improvement or recovery. Normal pressure, or hypertension, is a good prognostic sign. They find that diastolic pressure falls only in the very late stages. They emphasize the value of repeated blood pressure tests. Naucier (116) found hypotension in 60 per cent of his early cases. He concludes that low blood pressure is not a reliable sign of early tuberculosis. He finds that the low pressures seemed to be dependent more on the severity, than on the extent of the disease (toxemia?).

DeBloeme (117) studied 500 cases. In the group where the systolic blood pressure ranged from 100 to 110 mm, the blood pressure findings were of diagnostic importance. In the group with systolic blood pressure ranging from 80 to 100 mm ordinary diagnostic methods were all that were needed. He found a general relationship between higher pressures and better condition of the patients. The cases, in both sexes, showing systolic blood pressure of 110 to 150 mm had the most favorable outlook. He also found an association between low blood pressures and the occurrence of relapse, even after local signs had cleared and the general symptoms had subsided.

As to the causes of hypotension in tuberculosis Emerson's study (118) based on clinical and experimental evidence affords valuable data. His conclusions follow.

The causes of low blood pressure in tuberculosis are probably primarily a toxic action on the vasomotor center in the medulla, allowing of a vasoparesis or stimulating an active vasodilatation, and, secondarily, progressive cardiac atrophy or degeneration. Toxic action on the vasomotor nerves or their motor terminal or on the nervous mechanism of the heart cannot be positively denied, although there is no proof of it at present. Toxic action of tubercle products has not been demonstrated in the muscle of the vessel wall or heart, although with regard to the latter, the degenerated heart muscle found in advanced cases may have an influence in causing hypotension.

Rapid heart action is a usual and necessary sequel to low blood pressure, and will, if extreme, aggravate the hypotension by the very act of its shortened diastole. The hypotension of advanced cases may be due to the emaciation. Hypotension increases with the extent of the tuberculous process. Recovery from hypotension accompanies arrest or improvement. Return to normal pressure is commonly found in those who are cured. Continuation of hypotension seems never to accompany improvement.

TABLE 1  
*Artificial pneumothorax—single observations*

COLOR	SEX	AGE	CLASS*	SERIAL NUMBER OF PNEUMO- THORAX TO PATIENT	BLOOD PRESSURE BEFORE PNEUMO- THORAX	BLOOD PRESSURE AFTER PNEUMO- THORAX	BLOOD PRESSURE 24 HOURS AFTER PNEUMO- THORAX
W	M	26	F A	48	120/76	118/78	104/78
W	F	32	F A		120/90	110/80	
W	M	25	F A	52	92/54	102/54	
W	M	24	M A	38	134/64	135/58	
W	M	40	F A		110/64	110/64	
W	F	25	F A	46	104/66	106/70	120/88
W	F	19	F A	30	118/72	100/68	112/68
W	M	40	F A		110/70	110/70	
W	M	24	F A	40	106/60	116/62	116/68
W	M	25	M A		130/80	136/80	
W	M	30	M A		100/70	114/80	
W	M	28	F A		90/70	90/70	

\* F A, pulmonary tuberculosis—far advanced, M A, pulmonary tuberculosis—moderately advanced

Displacement of the heart, the result of adhesion, or lack of expansion due to cavity or adhesive pleurisy may be a causative factor of the tachycardia accompanying hypotension.

Certain complications of pulmonary tuberculosis are associated rather commonly with hypotension. Laryngeal and intestinal complicating lesions are instances in point. In tuberculous kidney lesions Reitter (119) found hypotension in contrast with non-tuberculous forms of pyelitis and pyelonephritis where the tension was normal or definitely increased.

Some authors have believed that blood pressure estimations might be used as a check to determine the amount of exercise allowed the

TABLE 2

*Artificial pneumothorax—repeated observations on same patients*

COLOR	SEX	AGE	CLASS	SERIAL NUMBER OF PNEUMO THORAX TO PATIENT	DATE	BLOOD PRESSURE BEFORE PNEUMO THORAX	BLOOD PRESSURE AFTER PNEUMO THORAX	BLOOD PRESSURE 24 HOURS AFTER PNEUMO THORAX
W	F	18	Γ A	31	11/16/25	106/62	104/60	104/60
				32	12/ 7/25	96/50	104/60	100/64
				34	2/12/26	106/70	110/72	
W	F	19	Γ A	42	11/ 6/25	118/54	116/46	108/54
				43	11/20/25	116/54	116/56	112/60
				44	12/14/25	110/60	100/74	100/60
				46	2/12/26	120/60	120/68	
W	F	19	F A	42	11/13/25	122/66	118/64	122/72
				43	11/30/25	110/64	120/72	112/74
W	F	19	Γ A	30	11/20/25	106/48	116/64	100/66
				31	11/30/25	102/52	98/62	92/54
				32	12/11/25	116/74	110/70	106/74
W	F	20	Γ A	37	12/ 4/25	94/64	100/74	92/60
				38	12/14/25	112/64	94/50	85/50
				40	1/24/26	120/70	98/54	
W	F	27	Γ A	16	11/ 9/25	122/98	128/86	126/90
				17	11/20/25	114/58	130/76	120/68
				18	11/30/25	104/56	118/78	102/64
				19	12/11/25	108/80	112/76	104/66
W	M	21	Γ A	1	11/ 2/25	124/60	98/44	110/40
				2	11/ 4/25	110/64	114/64	
				3	11/ 6/25	98/50	108/50	98/56
				5	11/13/25	108/50	112/54	106/56
				6	11/16/25	94/50	106/54	92/48
				7	11/20/25	102/62	98/58	100/50
				8	11/30/25	102/62	104/64	112/50
				10	12/ 7/25	90/45	104/56	100/64
				11	12/14/25	110/62	106/68	100/54
W	F	24	F A	38	11/ 3/25	112/58	118/54	114/62
				39	12/ 4/25	106/54	130/86	110/60
W	F	32	Γ A	35	11/ 6/25	134/66	134/68	130/74
				36	12/11/25	108/64	106/60	108/64



TABLE 2—*Continued*

COLOR	SEX	AGE	CLASS	SERIAL NUMBER OF PNEUMO- THORAX TO PATIENT	DATE	BLOOD PRESSURE BEFORE PNEUMO- THORAX	BLOOD PRESSURE AFTER PNEUMO- THORAX	BLOOD PRESSURE 24 HOURS AFTER PNEUMO- THORAX
W	F	42	F A	25	11/ 2/25	88/68	68/46	96/52
				26	11/13/25	96/64	98/72	96/70
				28	12/ 4/25	98/62	92/64	90/60
W	M	30	M A		2/ 1/26	130/90	120/80	
					2/15/26	100/70	120/80	
W	F	29	F A	23	11/13/25	98/60	110/72	112/74
				24	11/30/25	108/60	100/70	98/70
W	M	42	F A	35	11/ 2/25	138/70	142/78	125/88
				36	11/16/25	112/64	118/76	130/80
				37	11/30/25	110/64	126/70	120/72
				38	12/14/25	124/76	120/72	110/72
				40	2/21/26	140/90	150/80	
W	F	17	F A	38	11/ 2/25	112/74	122/72	115/82
				39	11/20/25	116/64	114/64	110/62
				40	12/ 7/25	98/68	100/64	110/66
W	M	29	F A	44	11/ 2/25	118/74	120/56	110/65
				45	11/16/25	112/60	124/62	120/70
				46	11/30/25	100/54	98/52	118/62
				47	12/14/25	112/60	100/50	108/68
W.	F.	27	F A	36	11/ 6/25	104/56	100/48	108/64
				37	11/20/25	104/56	106/76	112/70
W	F	18	F A	41	11/ 3/25	114/62	112/60	110/68
				42	12/ 4/25	100/60	106/62	102/56

\* F A, pulmonary tuberculosis—far advanced, M A, pulmonary tuberculosis—moderately advanced

tuberculous patient Peters (126) decreases the amount of exercise if the patient shows a drop of 6 mm or more after one hour's rest, or if exertion is immediately followed by a marked fall (10 to 20 mm)

The establishment of artificial pneumothorax, now so generally used in the treatment of pulmonary tuberculosis, is usually found to be without marked influence on the blood pressure Friedlander

has recently made a study of this point, using patients in the wards of the Cincinnati Municipal Tuberculosis Sanatorium. The majority of these cases come under the category of the far advanced, the others are all moderately advanced.

In the series studied there were no minimal cases. Tables 1 and 2 show that the induction of artificial pneumothorax is without constant effect on blood pressure. For part of the cases single observations of pressure (i.e., before, just after and 24 hours after pneumothorax) were made. For the rest, repeated tests were made on the same patient, at each induction of pneumothorax. As would be expected the tables show moderate hypotension in the majority of cases, but it is quite apparent that there is no constant variation due to the pneumothorax itself.

It is probably true that the long continued, and therefore often repeated collapse of the affected lung is of distinct value as an aid to the healing of a tuberculous lesion, so that gradually, after repeated pneumothoraces, the pressure may rise coincident with the general improvement. This overcoming of hypotension cannot however be ascribed to the induction of pneumothorax per se. It is to be remembered that symptoms of shock, and occasionally even sudden death, have followed the induction of artificial pneumothorax. According to Norns (127) such events are due to a pleural reflex which consists of afferent medullary impulses by way of the vagus nerve from its terminal filaments, which have been rendered unduly susceptible to stimuli as a result of compression or inflammation. Death is apparently due to vasoconstriction of the cardiac or cerebral vessels. Sachs (128) warns against the performance of artificial pneumothorax in the presence of severe cardiac complications.

Discussing the hypotension of tuberculosis, Burnand (129) says that it is a feature which adds considerably to the danger of the condition. When marked, he believes it makes the outlook very much worse. He believes that the routine, periodical administration of digitalis is of very great value in the management of pulmonary tuberculosis.

### *Syphilis*

The earlier view was that the hypotension sometimes found in the secondary stage of syphilis was associated with the resulting aortitis.

More recent studies, especially those of Warthin (120), have shown that the heart wall itself is involved. He finds that the essential lesion in the earlier stages is an interstitial myocarditis, characterized by infiltration with lymphocytes and plasma cells along the vessels between the muscle fibres. The entire heart wall from epicardium to endocardium, including the papillary muscles, may be involved in the infiltration. Eventually there is a progressive fibrosis of the heart muscle. Clinically it has been shown by recent studies that there is nothing characteristic in the blood pressure readings in the majority of cases of cardiovascular syphilis. Hypotension, when it does occur early, is in all probability dependent upon the factor of myocardial degeneration, resulting from the specific lesions as noted.

A form of syphilitic hypotension to which attention has been paid of late, is syphilitic lesion of the adrenals. Deaderick (121) gives a review of the literature in addition to his case report. A woman of 40 with positive Wassermann, developed among other changes, weakness, hypotension, anemia and marked pigmentation. A diagnosis of probable Addison's disease was made. After three weeks treatment with mercury and epinephrin, the systemic symptoms were improved. The pigmentation remained unchanged. A month after discharge the patient reported that the discoloration was fading.

Covisa and Bejarano (122) find that in subjects affected with syphilis, and in whom asthenia and pigmentation appear, hypotension is always present. They regard these manifestations as being due to luetic lesions of the adrenals. They advise the addition of epinephrin to the regular antiluetic treatment. Figueredo (123), in a study of the histologic lesions of the different organs in 90 autopsies on syphilitic persons, found lesions of the adrenals in 75 of the cases. The following disorders were seen: Lymphatic and plasmatic infiltrations, para- or sub-capsular, rarely cortical (63 per cent), thickening of the gland with perivascular infiltration (31 per cent), circumscribed fibrosis (33 per cent). Spirochetes were found in the zones of leucocyte infiltration. The author stresses the point that adrenal lesions were found in 83 per cent of autopsies on syphilitic subjects. Merklen, Devaux and Desmouliere (124) discuss the marked asthenia which occurs in some persons, in whom marked objective signs of syphilis are wanting, in whom the diagnosis is established by serodiagnosis.

This condition, according to these authors, has been described as syphilitic neurasthenia. They feel however that the syndrome probably rests upon an organic basis, and feel that there is warrant for the assumption that the adrenals may be the site of a definite luetic lesion. They find that specific therapy ameliorates the condition, and that, if persisted in, it may cure.

Clinical evidence, supported by histologic studies, would thus indicate that syphilis of the adrenals may produce marked hypotension. It is not to be concluded however that Addison's disease rests upon a luetic basis in many instances. As a matter of fact Levy-Frankel and Juster (125) as the result of their studies of syphilis of the sympathetic system find that cases of Addison's disease of proved syphilitic origin are rare.

### *Diabetes*

Diabetes, per se, apparently influences blood pressure very little. Rosenbloom (130) made routine estimations of the pressure in a series of 140 diabetics. Some of the cases were studied over a period of ten years. It appeared that the pressure in uncomplicated diabetes is normal or slightly under normal. *Hypertension* in this series was, in each instance, associated with such complications as aortitis, arteriosclerosis, nephritis, cardiac hypertrophy or aortic endocarditis. 16 of the 140 cases (22 per cent) showed such hypertension. The presence or absence of hyperglycemia had no effect upon blood pressure. In conditions of acidosis, the blood pressure fell. Koopman (131) studied the pressure in 161 cases, dividing them into seven groups, according to age in decades. He found that in young diabetics the blood pressure is normal, in older patients hypertension is the rule. In his series there was no relation between complication and blood pressure, except in the case of nephritis and arteriosclerosis. He also found that acidosis did *not* diminish blood pressure. Hitzemberger (132) also states that in young patients with diabetes the blood pressure, is, as a rule, somewhat lower than in normal individuals of the same age. Per contra, elderly diabetics show hypertension. Joslin (133) also finds that the blood pressure in diabetes is slightly below normal until the age of thirty-five is reached. Thereafter the pressure goes slightly above normal and the interval between diabetic

and normal persons widens as age advances. However, in a study of 500 cases of diabetes made since 1919, 35 (7 per cent) showed definite hypotension. The suggestion is made that the number of cases of hypotension had become greater in the period since undernutrition was introduced, and prior to treatment with insulin.

Kylin (134) (135) emphasizes the fact that uncomplicated diabetes in young people shows a normal blood pressure, while in elderly diabetics hypertension is the rule. In these elderly diabetics the blood pressure drops toward normal during sleep. There is no high capillary pressure. Working in Joslin's laboratory, Root, Thompson and White found an average drop of over 40 mm. in the pressures of elderly diabetics between 5 p. m. and 8 a. m. Diabetics without hypertension showed no fall during the night. Red counts in capillary and venous blood in the hypertensive diabetics showed evidence of capillary stasis in the afternoon and a fall in the capillary count during the night.

Maranon (136) found that in the pre-glycosuric period there is often a hypertension. As soon as symptoms of real diabetes appear the blood pressure sinks. He suggests that when a person of about 40 has hypertension with (or even without) hyperglycemia he is inclined to become diabetic, especially if he be very fat.

The probability of oncoming diabetes is heightened if the patient shows decreased carbohydrate tolerance. In a certain number of cases of diabetes there exists a preglycosuric stage of hypertension associated with itching, neuralgia, furunculosis, etc.

Recently there has been discussion as to whether insulin has a pressure lowering effect. This question is considered in the section of pressure lowering drugs and tissue extracts.

#### *Addison's disease*

Marked hypotension is one of the outstanding clinical features of Addison's disease, although, as has been shown recently, it is not invariably present. It is also generally admitted that the syndrome of Addison's is due in large measure to loss of function of the adrenal system. Pathologically, the principal lesion of the adrenals is bilateral caseous or fibrocaceous tuberculosis, with or without calcification. Occasionally simple atrophy of the adrenals is found, and

syphilitic lesion of the adrenals has been found in a few instances showing the typical Addison symptom complex. It is also true that a considerable proportion of persons attacked show the characteristic features of the lymphatic or thymolymphatic constitution.

Despite this knowledge, it is at the present time impossible to explain perfectly the hypotension of the disease in terms of dysfunction of one or of several of the factors which ordinarily maintain normal blood pressure. Thus, as McLeod (137) points out, it is not known whether adrenal cortex or medulla is at fault. The results of epinephrin administration do not support the view that the asthenia and hypotension are due to incompetency of the medulla. The view most generally held is that of Bittorf (138), namely, that Addison's disease is dependent upon a lesion of the whole adrenal body, medulla and cortex.

From this point of view, Hoskins's discussion of the relation of the adrenals to the circulation is of interest (139). He concludes, from a review of the literature, that the adrenals have a definite pharmacologic relation to the circulation by virtue of their production of epinephrin. Epinephrin causes stimulation of the heart, vasoconstriction in the splanchnic and cutaneous regions, and dilatation in the skeletal muscle. The cortex is probably the indispensable part of the adrenal. The medulla apparently serves merely to reinforce the nervous system in times of stress. But he emphasizes the fact that adrenal extirpation with its resulting circulatory collapse "is not entirely, if at all due to adrenin lack, since it cannot be long forestalled by the administration of the drug and it does not ensue when adrenin secretion is reduced below detectable limits." If one substitutes for "adrenal extirpation" "destructive adrenal lesion," there is the condition produced which is present in Addison's, and the same line of reasoning is, according to present day evidence, just as valid. The conditions producing hypotension in Addison's are understood—the mechanism of its production is still not clear.

With reference to the treatment of Addison's disease it is to be noted that substitution organotherapy was tried out as early as 1892 by Charrin and Langlois. Since this time this treatment, *faute de mieux*, has been tried by numerous clinicians. Good results have, at times, been reported.

Recently Rowntree (140) has advocated the treatment of Addison's disease by forced organotherapy. Epinephrin is given hypodermically and by rectum and whole gland or suprarenal cortex by mouth to the point of tolerance. This involves the determination of tolerance, which varies widely in each individual case. Once established, it becomes an index to dosage. The untoward effects of epinephrin, given hypodermically, are general weakness, tremor, and cardiac palpitation, by rectal injection, tenesmus. Over-dosage of whole gland or cortex by mouth causes gastric distress, nausea, vomiting, intestinal cramps. General supportive treatment is indicated in addition to the specific treatment. In another communication Rowntree (355) reports nine cases of Addison's disease, all treated by the administration of desiccated whole gland and epinephrin. Each patient experienced subjective improvement. The pigmentation decreased in all of the cases. Prolonged improvement was accompanied by increase in weight, decrease in the gastro-intestinal symptoms, and slight rise of blood pressure. Improvement began within one week after beginning treatment. Individual tolerance was raised markedly, and definite intolerance was encountered in some cases.

### *Food deficiency diseases*

Hypotension is common in some of the food deficiency diseases, though even when present it is not always severe. With reference to the explanation of the hypotension it is of interest to note that Bigland (141) studied many outbreaks of epidemic dropsy during the late war. These were associated with various pathological, and particularly with dietary, conditions. Bigland refers to McCarrison's studies showing that malnutrition (and particularly avitaminosis) leads to hypertrophy of the adrenals and thus to edema. McCarrison (142) has offered evidence to show that the enlargement, with increased epinephrin content, of the adrenals in inanition and in avitaminosis may be correlated with the acidosis associated with these states. Its occurrence for the most part during the terminal phases of avitaminosis, its association with marked respiratory disturbances, with anoxemia, with falling body temperature, and its rapid disappearance on supplying the missing vitamins, suggest that it is an emergency effort on the part of the adrenals to compensate for these changes.

Neuberger (143) studied 38 patients (33 male, 5 female) from 12 to 20 years of age showing post war late rickets and osteomalacia. He concludes that proper functioning of the endocrine system is necessary to normal calcium and phosphorus metabolism. He does not consider parathyroid dysfunction the sole cause of such disturbed calcium metabolism. He believes that lack of vitamins may be a primary factor in the production of this glandular dysfunction.

### *Bronchial asthma*

The theory of pathogenesis of bronchial asthma receiving most general support today is that the underlying factor is protein sensitization of the individual. The offending proteins may be exogenous (e g, asthma the result of food allergy), or endogenous (e g asthma the result of bacterial infection). At the same time it is generally admitted that certain other factors may play a causal rôle. The inheritance theory of bronchial asthma seems to have some foundation. Cooke and Venderveer (144) found a positive history of antecedent disease in a series of 500 patients with asthma and hay fever. Pollak (145) believes that the underlying factor is imbalance of the endocrine system. Klinkert (146) (147) thinks that in asthma there is a hyperfunctioning of the autonomic nervous system. The anaphylactic shock is due to a toxic split protein which, circulating in the blood, affects the autonomic nervous system. Alexander and Paddock (148) in a study of bronchial asthma found that a considerable proportion of asthmatics presented features of status lymphaticus. Many of the cases also showed abnormal reactions characteristic of vagotonia. They made a particular study of 20 cases with reference to response to pilocarpin and epinephrin. The majority of these cases reacted to the subcutaneous injection of epinephrin with an abnormal rise of blood pressure. They also showed other signs: pallor, tremor, sometimes rigor, which were taken to denote an increased sensitiveness to the drug. A relation between low blood pressure and excessive epinephrin reaction was apparent. The smaller number of cases with normal or high blood pressure gave regularly normal reactions. These cases which were found to react excessively to epinephrin were found to be relieved by 0.25 cc, a much smaller amount of the drug than is usually employed. Kerpolla (149) also



studied the action of epinephrin in asthma. He found a rise in blood pressure of 15 to 20 mm. in 75 per cent of his cases during the attack. The pressure fell at the end of the attack. On suppression of an attack with epinephrin, the blood pressure dropped promptly. He found that in asthmatics there is a hypersensitiveness to epinephrin which elicits a response after a dose ineffectual in normal persons. He believes that the action of epinephrin in arresting an attack of asthma is due to a paralyzing effect after the vasoconstriction.

### *Focal infections*

Focal infections arising from chronic inflammations of tonsils, teeth, accessory nasal sinuses, gall bladder, genitalia, etc., are very frequently accompanied by marked hypotension. Such hypotension is, of course, apt to be present for a long time. Hoxie (370) says that the most persistent types of hypotension, belonging to the infectious group, occur in cases of focal infection. He even thinks that the low pressure here may be a sign of diagnostic value. In cases of persistent low blood pressure one should suspect the presence of focal infection. In many cases of infectious arthritis, depending upon focal infection, the hypotension may be extreme. It is due to the very marked depression of vasomotor tone. It is to be remembered, also, that such vasomotor depression or exhaustion may persist for some time after the actual foci of infection have been removed. Enucleation of diseased tonsils, extraction of teeth having root abscesses, excision of infected gall bladders do not immediately restore the exhausted vasomotor tone. And it is a clinically established fact that persistent post-infectious hypotension is a symptom that is very frequently found. In some cases of focal infection direct damage is done to the myocardium, so that the cardiac factor enters into the production of the hypotension. Vasomotor exhaustion resulting from bacterial toxins is a more frequent cause of the hypotension from focal infections. In some cases a combination of the two etiological factors produces the low pressure and explains its persistence.

### *Non-infectious chronic arthritis*

While it is recognized that the majority of cases of chronic arthritis are infectious in origin, it is probably true that a small number may be

due to exhaustion or continued nervous strain or anxiety. Thus an association between exophthalmic goitre and rheumatism has long been recognized. And certain cases of chronic rheumatism do improve remarkably under thyroid therapy. Sergeant calls attention to the fact that in the cases of arthritis in association with endocrine dysfunction, it is the arthritis which first attracts attention. Careful previous examination, if there had been an opportunity, would have given evidence of endocrine abnormality. Thompson (150) groups cases of chronic arthritis into three classes, isotrophic or undifferentiated, atrophic, and hypertrophic. The cases of the isotrophic group represent the residua of primary foci. They may remain as such without bone changes or may develop the lesions of the other groups. In this event, endocrine dysfunction may be demonstrable as a direct or a contributing etiologic factor. The cases of the atrophic group offer some evidence of endocrine dysfunction. In many, features of dysthyroidism are present. Occasionally in the atrophic group other endocrine foci are active. The cases of the hypertrophic group show evidence of endocrine dysfunction, apparently of the thyroid. There is low metabolic rate, bradycardia, hypotension and generally lowered physical tone. These cases are often amenable to gland therapy. Such observations as these have been reported from various sources. Our present still inexact bases for organotherapy, demand that they be carefully confirmed before the conclusions drawn be accepted as entirely valid.

### *Anemia*

The hypotension which is due to hemorrhage has already been discussed. The chief factor here is the reduction of blood volume. In marked anemia, not due to hemorrhage however, the blood pressure is also apt to be low in proportion to the cachexia and general weakness. Cabot says that in pernicious anemia pressures of 80 mm. and even 60 mm. are not unusual. Wiggers (151) finds that there is a curious relation between minute volume and peripheral flow in severe anemias. This condition is less marked in chlorosis than in other severe anemias. Plesch found that the minute volume of the heart is increased in the anemias, while Stewart found the peripheral flow in anemia less than normal. Stewart regards these changes as a

compensatory effort on the part of the peripheral mechanism to divert blood from the periphery to more vital organs. In this way the return of the blood to the heart and lungs is assisted, in that the circulation time is shortened. Fahr and Ronzome (152) made microscopic examination of the skin capillaries in a case of pernicious anemia. These capillaries were contracted to half or less than half the normal diameter. A lessened flow through the skin and a greater flow through other organs was thus determined.

### *Cachexia*

Nutritional failure from any cause is often associated with hypotension, though this is not invariably the case. In advanced cachexias hypotension is the rule and may become extreme. Ewing (153) in discussing the emaciation accompanying growth of malignant tumors says that it occurs early or late, with or without anemia, though probably always with diminution of blood volume. It is preceded by distinct muscular weakness. It affects chiefly the muscular system, also, to a lesser degree, all cellular organs and tissues. Inanition is probably the chief factor in the loss of weight. The mental depression, which is so common, leads to a distaste for food, with lowering of the digestive capacity. In the growth of the majority of malignant tumors there is associated a progressive deterioration in the quantity and quality of the blood. The hypotension, accompanying such conditions could of course be explained on this basis. It is, however, altogether probable that the cardiac factor enters into consideration where life is prolonged long enough, indeed heart failure from myocardial degeneration is common in late cachectic stages.

Ewing also refers to the fact that in certain carcinomata, particularly of the stomach, the anemia resulting from repeated hemorrhages or even occurring without them, begins to dominate the picture, and takes on a secondary pernicious form. The hypotension of cachectic states is to be explained on the basis of one of these factors, or of combination of several of them.

## HYPOTENSION IN CERTAIN CONSTITUTIONAL DIATHESES

*Status lymphaticus*

Status lymphaticus is a constitutional anomaly whose outstanding features are hyperplasia of the thymus, hyperplasia of the lymphoid tissues in various parts of the body including tonsils, pharyngeal lymphoid ring, lymph nodes and lymphoid tissue of the intestinal follicles. With this there is splenic enlargement. In addition there is marked hypoplasia of the cardiovascular system and developmental deficiencies in the genitalia. Clinically two types may be recognized. In true status lymphaticus the individual is generally underproportioned, with particularly clear skin and transparent sclerae. Here the underdevelopment of lymphoid tissues is most marked. In recessive status, there is atrophy of the lymphoid tissues. In true status, the thymus is hyperplastic, or in older individuals, persistent. In recessive status this is not the case in the majority of cases (Friedlander (154)). Hypotension in such cases is the rule.

The condition, originally described by Paltauf in 1889, had been considered to be of infrequent occurrence. Recent studies have shown the falsity of this view. In 1918 Symmers (155) showed that in Bellevue Hospital 457 cases of status lymphaticus were encountered in 5652 autopsies (8 per cent). The first 249 cases of status lymphaticus were carefully analyzed by Symmers. In 118 cases of true status, the thymus was hyperplastic in every instance. In the recessive state this was not true. In 70 of the 89 recessive cases the thymus was not visible to the naked eye. In 51 of the 249 cases the heart was smaller than normal. In 40.5 per cent of these same cases the aorta was hypoplastic. It has long been known that individuals of this lymphatic type stand the toxemia of acute infections very badly, and it is therefore of interest to note that of the 249 cases analyzed by Symmers, 222 (88 per cent) showed some form of acute infective lesion at autopsy. Of these the commonest were endocarditis, pneumonia and meningitis.

The hypotension in status lymphaticus is to be explained partly on the basis of the cardiovascular hypoplasia with its resultant diminution in driving power. It may also stand in relation with the hypoplasia of the chromaffin system which is, in all probability, part of this diathesis.

*Infantilism*

Infantilism is a condition where there is lack of development of the individual both corporeally and psychically. Various types have been described. Lorain described a form characterized by general arrest of development rather than involvement of any special organ or system. Brissaud described a type where, due to an anomaly of development, the morphologic characteristics pertaining to infancy and early childhood persist beyond the ages at which they should normally be found.

In both of these types hypotension occurs, in varying degrees. In the true dystrophic form (type Lorain) the etiologic factors are toxemia, or disease arising in intrauterine life or in infancy (Goetsch (156)). In the second group, belonging chiefly to the Brissaud type, the infantilism is caused by primary disease of one or more of the ductless glands. Even though one of the ductless glands is chiefly involved, as in the cases of the myxedematous type resulting from some form of dysthyroidism, there are apt to be secondary disturbances in other glands. The type illustrates the fact that a proper interplay of function of all the ductless glands is necessary for proper growth and development. In some cases there are several glands involved, true pluriglandular dystrophies.

*Myasthenia gravis*

In a discussion of myasthenia gravis, Dana (157) reports fourteen cases. The clinical and pathological grounds for belief in an endocrine etiology are referred to, though no experimental evidence is adduced. Dana emphasizes the frequency of mild prodromal seizures, the frequently prolonged and favorable course of the malady. One of his patients had five attacks in seventeen years and recovered. Another had four attacks in eighteen months and got well. He notes the presence of myotonia (muscle spasm) in some cases, a feature not generally alluded to in the literature. Bell (158) from his study of the literature has found that hyperplasia or tumor of the thymus is present in 50 per cent of cases of myasthenia gravis coming to autopsy and reported since 1901. Mella (159) finds that involvement of the thymus occurs in some cases of myasthenia. Irradiation of the thy-

mus is followed by marked improvement. In some cases the clinical symptoms of myasthenia disappear completely after x-ray treatment of the thymus. Pierchalla (160) reports a case of myasthenia with large thymus shadow. Under x-ray treatment the thymus was shrunk. The symptoms and the myasthenic muscle reactions disappeared. In his original work on the treatment of enlarged thymus by the x-ray, Friedlander (161) showed, experimentally, that a thymus partially involuted by the action of x-ray, is capable of regeneration. It is quite possible that variations in the degree of thymus hyperplasia may occur spontaneously, and thus might well account for the remissions and exacerbations of symptoms of myasthenia as reported by Dana and others, in some cases. At this time it cannot be stated positively that myasthenia is always dependent upon thymic lesion. Thus Lecaplain and Billiard (162) find that in cases of myasthenia of the amyotrophic type, there are evidences of adrenal insufficiency.

### *Adiposis dolorosa*

Dercum was the first observer to note the peculiar fat deposits and the pain. Vitaut showed that asthenia and psychic manifestations were parts of the picture. Recent post-mortem studies have shown fairly constant changes in the thyroid, hypophysis and sex organs, in frequency in the order named (Sprunt (163)). Marine believes the essential lesion to be an atrophy of the thyroid. The asthenia has been ascribed to lesions of several of the ductless glands, the thyroid, hypophysis or adrenals. Waldorp (164) says that the muscular and cardiovascular asthenia can be attributed to disturbances of the adrenals or the vegetative nervous system, central or peripheral. Winkelmann and Eckel (165) report one case and review fifteen cases cited in the literature. The authors' own case, at autopsy, showed pathologic changes in the pituitary, adrenals, and ovaries. The necropsy findings in the fifteen cases from the literature showed pluri-glandular involvement in thirteen cases. Only two showed no definite changes in the ductless glands. Of the eleven patients in whom the pituitary was examined, eight showed pathologic change. The thyroid was abnormal in twelve of the thirteen cases, the sex glands in nine, the adrenals in three, the pancreas in two. From a clinical

standpoint it is of interest to note that the condition is five times more prevalent in the female. Most cases develop after the age of thirty-five. The theory of endocrine malfunction seems best suited to explain the symptoms, including the asthenia. Engelbach (166) has made a careful study of the various types of endocrine adiposity, based upon a study of 1995 cases of disorders of the ductless glands. As aids in the diagnosis of the gland involved, the age incidence of the obesity and its localization and distribution were depended upon. The fact is emphasized that many cases of endocrine adiposity begin as a uniglandular disorder. To yield best results treatment must be instituted early, when only one gland is affected, for the purpose of stimulating it to normal physiologic activity. Failure in treatment is due to late diagnosis, and a lack of knowledge of precise therapeutic indications. With the exception of thyroid preparations, organotherapy by mouth is unsatisfactory. One common cause of failure with organotherapy is insufficient dosage.

#### HYPOTENSION DUE TO CERTAIN MECHANICAL FACTORS

##### *Postural change*

Studies in postural hypotension have been made by various observers. The change in position of the body from the recumbent to the erect position throws a definite strain on the organs of circulation, determined by the gravitation of the blood. The physiological reaction is manifested by change in pulse rate and blood pressure. Normally, on change from the recumbent to the standing position, the splanchnic vasomotor tone overcompensates the hydrostatic effects of gravity. In general, for both men and women, the blood pressure response upon assuming the erect from a supine position is a slight drop in systolic pressure, a slight rise in diastolic pressure, and a rise in pulse rate. The pulse pressure, of course, diminishes. Mortensen (167) from his studies of normal and diseased persons finds that a drop of more than 6 to 8 per cent in the systolic blood pressure on change of posture, recumbent to erect, is evidence of myocardial inefficiency. The rise of the diastolic pressure is an index to the response of the vasomotor mechanism to assist the heart in maintaining circulatory equilibrium against the force of gravity. Crampton

(168) does not agree with these conclusions. He believes that a rise in the systolic pressure on standing indicates efficiency in the gravity resisting ability of the circulation, in proportion to the increase. He has worked out an index of these two changes, and believes that such an index may be of both diagnostic and prognostic value in studying conditions of circulatory deficiencies. Minus indices are to be taken as evidence of great lack of circulatory power. Commenting on Crampton's so-called "blood ptosis," a test of vasomotor efficiency, showing a marked decrease in systolic pressure and a marked rise in pulse rate, Schneider (169) found that the Crampton test was inaccurate on account of its neglect of various factors. In his work on determining physical fitness, largely in candidates for aviation, Schneider rated a man on the reclining pulse rate, standing pulse rate, the increase in pulse rate after exercise and the time required for return to the previous norm, and the difference between the systolic pressure reclining and standing. Sewall (170) laid particular stress on the rise in diastolic pressure which accompanies the change from recumbent to erect posture. In normal cases, and occasionally in pathological conditions, the systolic pressure does not change, sometimes it even shows a rise. According to Sewall excessive fall of systolic pressure in the erect posture shows weakness of vasomotor control. Excessive rise of diastolic pressure denotes vascular spasm and abnormal effort. Adequate pulse pressure is necessary to maintain nutrition of the brain and other tissues. He found that individuals in whom there is excessive gravitation of blood to the extremities and the splanchnic area on standing are the victims of physical weakness and nervous instability. They suffer from headache, dizziness and tinnitus while in the erect posture. Increase in the diastolic pressure and a drop in the pulse pressure are to be used as measures of physical fitness. Sewall believes that abnormal elevation of the diastolic pressure is the usual cause of the lowered pulse pressure in the erect position. He postulates the dictum that a high diastolic pressure with a vigorous heart beat indicates cardiac hypertrophy, while a high diastolic with feeble heart beat means cardiac dilatation. Stahnke (171) reports experiences which demonstrate that the position on all fours restores the primal physiologic position for the circulation. The demands made on the circulatory apparatus seem to be less in this position.



than under other conditions. Blood pressure may drop 8–10 mm below the normal figure for the individual in the erect position. In heart disease, therefore, Stahnke concludes that it might be well to have the patient do creeping exercises to strengthen the tone of the heart when ordinary gymnastics are too much of a strain. The blood pressure rises in animals when they are made to stand on their hind legs. In one instance reported by Hill the animal died from the circulatory disturbance. A very careful study of three cases of postural hypotension has been made by Bradbury and Eggleston (172). It is obvious that the value of carefully controlled, frequently repeated studies on even a limited number of patients is very great. The findings in these cases are therefore here summarized in some detail. The three cases, a white male of 39, a white male of 50, and a white male of 67 were similar in almost every detail. The complaint of each was the occurrence of syncopal attacks during or after exertion, or even after standing erect for some minutes. Other features were slow heart rate unchanged by postural variations in the blood pressure levels. The patients also showed inability to perspire, lowered basal metabolism and indefinite changes in the nervous system. Each of the patients felt much worse during the heat of the summer. One patient was made to exercise for the purpose of noting effect upon respiration and pulse rate. Upon sitting down after exercise no dyspnoea was noted and no tachycardia. After a minute the head fell back, pupils dilated, there were slight convulsive movements, pallor and unconsciousness. In five minutes consciousness was restored. Five minutes later blood pressure was 60/40 mm. A fortnight later the effect of change of posture on blood pressure was studied. The figures were, supine 105/60, standing 40/28, sitting 42/20. On various occasions, when standing, systolic pressure as low as 35 mm. was noted. Regardless of position the pulse rate was always slow, 60 to 66. Electrocardiogram showed no abnormalities. Basal metabolism was minus 21 per cent. This case also showed a marked nocturnal polyuria. There was in addition a moderate and gradually increasing anemia, with normal leucocyte and differential count. Negative blood and spinal fluid Wassermann. Blood sugar was normal, occasionally below normal. Urea nitrogen was always at the upper limit of normal. This patient was alive, unchanged, after

nearly six years observation. The other two cases presented almost the identical picture. The second patient died suddenly during a hot spell, after three years study. The third patient was alive and unchanged after four years. The points to be explained in these cases, according to the authors, are the persistently slow heart rate and the remarkable behavior of the blood pressure. Disease of the adrenals is excluded by the authors because all the typical symptoms of Addison's disease (except asthenia) were missing. There was no progression. Toxic hypoadrenia would be excluded by the length of the clinical course. Hypochromaffinism is excluded by the absence of evidence of congenital inferiority and the total lack of characteristic symptoms.

There was no evidence of heart block, either complete or partial (electrocardiograms and administration of atropin). The lack of increased heart rate under atropin would exclude heightened vagal activity. During the syncopal attacks the heart rate and rhythm did not change.

Epinephrin raised the pressure temporarily in these cases. The outstanding feature in them was the marked dependence of the systolic and diastolic pressures upon the influence of gravity, as exerted through alterations in the positions of the body from the horizontal. The reactions were those to be expected if the whole peripheral vascular bed were always wide open, inelastic, and capable of accommodating the major portion of the entire blood volume of the body.

The authors present the following suggestions as to etiology:

(a) These three cases showed a total loss of peripheral vascular tone, and a loss of the normal mechanism by which blood pressure is maintained in different parts of the body.

(b) There seemed to be some extensive disturbance in the functional activity of the vegetative nervous system.

(c) The heart rate was uniformly slow, unaffected by the large changes in blood pressure following change in position of the body.

(d) The sympathetic acceleration control of the heart was impaired. Atropin did not accelerate the heart rate, and pronounced fall in blood pressure caused no compensatory increase in rate.

(e) The responsiveness of the vagus to pronounced elevation of blood pressure (posture and epinephrin) seemed to be largely wanting.

(f) Both cardiac accelerator and augmentor functions of the sym-

pathetic can be stimulated by epinephrin. In these cases such stimulation did not restore the capacity to maintain the blood pressure level in the face of the influence of gravity.

(g) The responsiveness of the vasoconstrictor endings of the sympathetic to stimulation by epinephrin was much impaired or entirely lost.

(h) The inability of these patients to sweat was not due to defect in sweat glands or to lack of their ability to respond to pharmacological stimulation of the sympathetic endings. Neither could it be attributed to the abnormally low blood pressure.

(i) Efforts to cure these patients or control their disorders were unavailing. These efforts included the administration of thyroxin, epinephrin, dried suprarenal substance, mixed glands, strychnin, digitalis and the enforced consumption of sugar and of water.

(j) Paralysis of the sympathetic vasoconstrictor endings seems to be the only adequate explanation of the blood pressure reactions observed. It accounts for the absence of vasoconstriction after exhibition of epinephrin. It also explains the total absence of the normal vasomotor control by which blood pressure is maintained at a nearly constant level in the face of changes in the position of the body in normal persons.

### *Body habitus*

Glenard's description of enteroptosis as a pathological entity appeared about forty years ago. From that time on, and particularly since the use of the x-ray in the diagnosis of gastrointestinal diseases, medical literature has teemed with articles on dropped stomach, ptotic intestinal viscera and the dangers resulting therefrom. Congenital and acquired forms have been described. The general line of reasoning followed has been the always dangerous, and often fallacious, one of *post hoc ergo propter hoc*. It does not follow that an individual who has a stomach lying low *and* indigestion, has that indigestion *because* of the position of his stomach. Moody, Van Nuys and Chamberlain (173) studied the position of the stomach in 600 picked students in the University of California. All of them were healthy, a third of them were athletes. None had dyspepsia. These persons were radiographed in the standing position. In 74 per cent

of the men, and 87 per cent of the women, the greater curvature of the stomach was found below the inter-iliac line. Neither was there found any constant relation between the shape and position of the stomach and the strength and build of the individual. The transverse colon was most commonly situated in the pelvis. Carefully made studies such as this must convince one that the drawing of sweeping conclusions as to fixed relations between body build and body function are, to say the least, hazardous. For a refreshingly clear and reasonable presentation of enteroptosis, reference may be had to Alvarez's article (174). Larimore (175) using Mills's classification (176) has made a study of blood pressure in relation to types of body habitus. He investigated a group of 417 factory workers. In this group the sthenic habitus shows a higher blood pressure than does the asthenic. The pressure in the hyposthenic groups was intermediate. The average blood pressures were approximately the same for male and female asthenics (males 106/63, females 105/68). Hyposthenics are also approximately the same (males 116/71, females 115/72). The sthenic group showed somewhat higher pressures for males, (males 126/78, females 118/73). These relations do not change when types are separated into groups for age decades. There was found a very small direct correspondence for body surface and the decreasing blood pressure. Martini (177) says that in the examination of about a thousand patients in two years he found 108 presenting a combination of constitutional asthenia, sagging of the viscera, and weak circulation. He believes that there is some common cause, which he does not state, for this condition. In 92 per cent of these cases there were complaints of disturbances in the digestive apparatus, usually in the stomach. He says that treatment must be directed toward each of elements in the triad, adding the significant comment that the frequently underlying congenital lues, tuberculosis or alcohol addiction must be considered. He found that repeated pregnancies and emotional strain seemed to be responsible in some cases, while a familial predisposition was sometimes evident. Discussing the reactivity of asthenics Barath (178) found that persons with an asthenic habitus produced lower agglutinin titers after injections of typhoid vaccine, than other patients.

*Effects of exposure to high temperature upon circulation in man*

Recently Adolph and Fulton (179) have made this question the subject of renewed experimental study. Their paper includes a review of the literature, with appended bibliography. They conclude that

1 Exposure to high temperature increases the loss of  $\text{CO}_2$  from the blood, through the skin and lungs. This lowering of carbon dioxide tension increases the hydrogen ion concentration of the blood and ultimately leads to an excretion of alkali from the blood. The carbon dioxide dissociation curve of the blood is not significantly altered.

2 The peripheral blood vessels are greatly dilated during exposure to high temperature and this dilatation continues indefinitely. The lack of a high resistance in the peripheral blood vessels prevents the blood from returning to the heart.

3 The heart rate increases steadily and rapidly and is even able to increase the systolic blood pressure. In spite of this compensating activity on the part of the heart, the blood flow back to the heart finally becomes inadequate. At this point circulatory failure or shock is complete, with faintness.

4 The rise in skin temperature seems to play the irritating part in control of the respiratory and circulatory reactions.

The low blood pressure in cases of heat exhaustion and certain of the milder cases of insolation, is accompanied by the general picture of shock: the skin is pale, cold, clammy and there is often profuse perspiration (180). Among others, Woolley (181) found that in every case of heat exhaustion there is a large initial loss of water. The hypotension in heat exhaustion would thus appear to be due to lack of peripheral resistance, and probable diminution in blood volume, the reaction being somewhat similar to that found in shock.

With reference to the effects of tropical sunlight on white men Norris points out that the deleterious effects are not due to blood pressure changes. The average blood pressure of whites in the Philippines is quite similar to that when at home. The slight fall, average 3 mm, comes during the first three months of residence and during the hottest months, as Chamberlain (182) found in his studies of blood pressure and pulse rates of healthy white males in the Philippines.

*Variations in atmospheric pressure*

It seems to be generally agreed that the disturbances of physiologic function resulting from high altitudes result mainly from deficiency of oxygen. The numerous careful studies made by Haldane, Henderson, Barcroft and others have shown the remarkable adaptability of the normal human mechanism to changed and changing conditions of barometric pressure. The symptoms caused by rapid ascent to high altitudes, vertigo, mental confusion and fatigue, can be abated by inhalations of oxygen. Blood pressure studies at high altitudes have shown that there is a primary fall of arterial pressure, but it is not marked. After acclimatization has taken place, the blood pressure tends to return to normal. The initial drops are more marked in hypotensive individuals than in those with ordinarily normal pressure. Sewall (183) points out that while life at high altitudes appears to involve no special change in arterial pressure, it is to be expected that the increased ventilation of the lungs especially during muscular exertion, would lead to a notable increase of the blood aspirated into the right heart. This would tend to induce overstrain of the heart when it is incapable of compensation.

Detailed discussion of the effects of high altitudes on persons healthy and diseased, (e.g., with pulmonary tuberculosis or cardiac disease) would take the present writing too far afield. Recently there have been some interesting discussions as to blood pressure during aviation. Cruchet (184) finds that under low air pressure at high altitudes, the arterial pressure in the flyers increases. The pressure becomes normal and all other phenomena of flight sickness disappear as soon as oxygen is inhaled. He asserts that the influence of oxygen is still manifest at an altitude of 26,000 feet (8000 metres), and probably even higher. Even the untrained, he says, can bear without harm an air pressure corresponding to an altitude of 8000 metres, if they inhale oxygen regularly. He gives charts showing the regular rise and fall of the blood pressure above and below normal, as the atmospheric pressure in the air chamber is varied to correspond with very high altitudes or with sea level.

Flack (199) reports a series of studies in candidates for aviation and on fliers themselves. In addition to the usual tests, including

the rotation test, observations were made on the ability of the candidate to raise a column of mercury by blowing, and then with breath held, support the column of mercury. The abdominal effort necessary to sustain the mercury increases the abdominal press. In subjects with a tendency to abdominal pooling, this pressure drives the blood on to the right heart, causing an increase in pulse rate and a rise in systolic pressure. The combined tests in Flack's series showed that in fit persons the tests produced but little effect on pulse rate or blood pressure. In cases subject to vertigo, nausea, etc., there was a marked acceleration of pulse rate and a rise in both systolic and diastolic pressures. Subjects who are liable to fainting, who have an unstable vasomotor system, show a marked, almost characteristic, fall in the diastolic pressure. And finally the conclusion is reached that, as the result of many studies, the satisfactory pilot is he who is relatively stable in his responses. Benjamin (200) refers to two series of tests now applied to candidates for the United States Air Service. One test is given in a so-called low pressure chamber. This is a steel chamber large enough to accommodate five or six persons. It is air tight. It is provided with chairs, tables and oxygen tubes. An operator gradually diminishes the oxygen pressure within the chamber. The examiner watches the nominee, who is instructed to take oxygen as needed. The prospective aviator is thus gradually brought under conditions equivalent to those of heights of 20,000 feet, by diminishing the oxygen tension, and the effects on him recorded. The other method of testing consists of the use of a Henderson rebreather apparatus. By appropriate mechanism the same air is rebreathed, with the  $\text{CO}_2$  constantly removed, the oxygen tension being thus gradually reduced. By this method the aviator's "ceiling," i.e., the height at which he can safely fly, is recorded. Detailed studies of reactions including blood pressure studies, are soon to be forthcoming.

#### THE ACTION OF TISSUE EXTRACTS, GLANDULAR EXTRACTS, AND CERTAIN DRUGS, ON BLOOD PRESSURE

In the consideration of this subject it is to be borne in mind that the hypotension induced by the introduction of these substances is, in many instances, a relative one. The reduction of hypertension by chemical means, by the action of tissue extracts or drugs, has been

made the subject of much study. Some of the work has been experimental and carefully controlled. In other cases the results have been achieved empirically. Subsequent work has sometimes justified the hopes raised by overenthusiastic empiricism, sometimes subsequent study has shown the falsity of the claims advanced, perhaps by offering a physiologic or pharmacologic reason for the failure.

From time to time, also, there have been efforts to raise the pressure of hypotensives by the administration of drugs. All this by way of explanation for the inclusion of this phase of the subject in a discussion of hypotension.

Details of pharmacologic data as to action of various hormones and drugs have been abstracted from various sources, Cushny (208) being especially freely consulted.

It is of course to be understood that no attempt is made here to include a discussion of all drugs that effect blood pressure. The effects in the case of some drugs are too slight or too transient to warrant discussion here.

#### *Depressor action of tissue extracts*

It has been known for many years that various tissue extracts have a depressor effect on blood pressure. As long ago as 1895 Oliver and Schaefer (185) demonstrated such depressor effects from aqueous and glycerine extracts of thyroid, parotid, submaxillary glands and the spleen. In 1909 Popielski (186) called attention again to the depressor action of organ extracts. He described a substance to which he gave the name "vasodilatin," which could be isolated from stomach, small and large intestine, brain, pancreas and thymus. In 1911 Barger and Dale (187) proved that histamin was present in the mucosa of the small intestine, in Popielski's vasodilatin, and in commercial peptone. In 1915 Fawcett, Rogers, Rahe, and Beebe (188) isolated a residue from the thyroid, alcohol-soluble. This had a marked depressor action. Its activity apparently bore no direct relationship to its nitrogen or iodine content. In 1919 Abel and Kubota (189) studied tissue extracts and their depressor effects. They brought forward evidence to show that histamin is a widely distributed constituent of animal tissues, organ extracts and enzymatic products, derived from animal or vegetable protein. It is probably not true



that histamin is the only constituent of tissue extracts capable of lowering blood pressure. Thus, Hanke and Koessler (190) have shown that typical peptone shock can be produced by the injection of peptone from which histamin is absent. It is also true, in all probability that the active principle in the depressor liver extract, to be discussed presently, is *not* histamin.

There would seem to be no doubt, however, that various tissue extracts do contain substances having a blood pressure lowering effect. This fact has been corroborated by a number of investigators. The outline sketched above could be amplified by the citation of the work of numerous other investigators.

#### *Liver extract*

In 1922, Levin (191) detailed his results after the use of hypodermic injections of liver extract. In three cases, marked reduction of blood pressure followed. In 1923, McDonald (192) (193) conceived the view that the liver secretes a substance which plays an important part in the regulation of blood uric acid. Killian and Kast had shown a definite increase in the blood uric acid of 80 per cent of cases of internal cancer. Mann and Magrath had found the blood uric acid steadily mounting, up to death, in dogs from which the liver had been removed. McDonald felt that if the substance regulating uric acid formation could be recovered from the liver, it might be of significance in the treatment of cancer. In the year following he made many extracts of liver and tested their toxicity in dogs and cats. Later he noticed that the blood pressure fell steadily in two cases of carcinoma, where the liver extract was being used to reduce the blood uric acid. Mindful of the fact that liver extracts and other tissue extracts had been shown to have depressor effects on the blood pressure of experimental animals, McDonald determined to try the effect of liver extract in a patient with hypertension. The encouraging result that followed led him to extend his observation to other patients. Thirty-three clinical cases were studied in all. In twenty-five cases the patients experienced no disagreeable symptoms. Most of them reported relief from the unpleasant symptoms of hypertension. The ages of the patients studied ranged from 45 to 67 years, with an average of 61 years. In these cases hypertension had persisted for vary-

ing periods, averaging six years. The average blood pressure before injection was 204/114 mm. In eight cases there were reactions of varying intensity, some of which closely resembled protein shock. There was an average fall in the systolic pressure of 62 mm, so that the average systolic pressure after injection in the thirty-three cases studied was 142 mm. The average fall in diastolic pressure was 28 mm, average diastolic pressure after injection 82 mm.

In cases free from symptoms, one injection served to depress the blood pressure from one to three or more days, according to size of dosage. In all the favorable cases the return to hypertension was gradual. In his original communication, McDonald stated that the chemical nature of these liver extracts had not yet been ascertained, though the experimental evidence indicated that the active material is not a protein. Every effort looking to the possible amelioration of so widespread and so difficult a condition as hypertension is worthy of careful consideration. The dangers attending the use of crude tissue extracts are so manifest, that it is evident that every effort should be made to find the active depressor substance in tissue extracts. Studies of the liver extract are at this time under way. Preliminary reports of such studies have been made by James and Laughton (194) and by James, Laughton and MacCallum (195). Their studies seem to show clearly that the active substance is nonprotein in character. It does not give the biuret reaction. It is soluble in 80 per cent alcohol, can be separated from accompanying pressor substances, and can be further purified through its solubility in ether. On experimental animals it has been shown that it will reduce blood pressure to a very low level (about 50 mm Hg), and that by its continued use the pressure can be maintained at such a level for an almost indefinite period. Larger doses reduce blood pressure to lowest levels and death ensues. These studies also showed that the active depressor principle in liver extracts is not histamin and not cholin. Its effects on blood pressure, in experimental animals, differ markedly from those obtained by those substances. Chemical tests for histamin and cholin in the isolated substance were absolutely negative.

The degree of effect produced on rabbits is dependent upon the dosage and strength of the extract. Overdosage kills the animals in

one to two minutes, without convulsions. At autopsy the heart and lungs of the animals appear normal. The blood seems to have collected in the large vessels. In rabbits anesthetized with urethane, no pressor substance being given, the fall in blood pressure and its duration vary with the dose of extract given.

For the last two years Major (196) has been studying hypertension. Major and his colleagues investigated some of the better known metabolites. They found that creatin and creatinin had no effect on blood pressure, but that methyl guanidin, a product of protein metabolism, would raise blood pressure promptly and that the rise would be maintained for several hours. Attempts were then made to determine the effects of certain substances on the hypertension produced by guanidin. *Veratrum viride* and amyl nitrite produced transient lowering. Calcium chloride produced a permanent fall in pressure accompanied by marked cardiac irregularity. This irregularity was overcome by the addition of potassium chlorid to the calcium chlorid. If the combination of potassium and calcium chloride were introduced before the administration of guanidin, the rise in blood pressure did not occur. A fall in blood pressure after guanidin administration was also secured by the injection of normal hydrochloric acid and ammonium chloride. The action of tissue extracts was also studied. Extracts of liver, spleen, kidneys, muscles, ovaries and testes were used. Some striking effects were obtained by the use of these tissue extracts, particularly with those from the liver. After considerable experimentation with various methods of extraction, Major and his colleagues have obtained a liver extract which has a marked depressor effect in certain cases of hypertension. As used by these observers, the extract contains no recognizable amounts of cholin, histamin, or peptone, and its pharmacologic action differs in most respects from that of these three substances. Some index of toxicity was obtained by injecting it into dogs whose blood pressure had been experimentally raised by guanidin compounds. The extract was found to have very little toxicity. In doses usually employed therapeutically no marked depressor action on the normal blood pressure of healthy persons was obtained. Forty-two patients with hypertension were treated with the liver extract. In three cases of hypotension, with pressures respectively of 100/64, 90/40, 95/70, the injections of the

extract were without effect on the blood pressure. It has been given in varying doses, 1 to 5 cc. Injections were made intravenously, intramuscularly and hypodermically. Some patients received daily doses, others were given one dose a week. Within an hour after injection, especially intravenously, the pressure falls from 20 to even 70 mm Hg. The fall is gradual and is, as a rule, unaccompanied by symptoms. Occasionally patients who have had a very marked and rapid fall complain of slight dizziness. The duration of the fall varies from several hours to several days. The type of patient who has responded most promptly to the injections has been the comparatively young person without evidence of renal damage or arteriosclerosis. Major emphasizes the fact that conclusions as to the therapeutic value of such a preparation can be drawn only by study of a large number of patients over a long period of time. Patients with hypertension often show great variations in pressure due to nervous influences, cardiac complications, etc. Further study of the liver extract is needed to show whether it will prove to be actually valuable in the management of cases of so-called malignant hypertension, or whether its effectiveness is limited to the benign group which frequently responds to regulation of the general regimen, with the addition of proper drug and dietary treatment.

Roger (197) (198) secured various liver extracts, depending on the processes used. Some fractions had depressor effects, some caused elevation of blood pressure. He succeeded in isolating a substance from the liver which apparently chiefly influences the heart action. Its effects on the heart were studied by the electrocardiograph. By alkaline hydrolysis, Roger secured a liver extract which produced sinus-bradycardia. Notwithstanding the constriction of the blood vessels after its injection, which should have caused hypertension, there was a marked fall in blood pressure. Roger believes that some of these substances may play a part, particularly in cardio-hepatic disturbances, by their introduction into the blood stream in minute amounts following cell destruction, just as they occur in extracts obtained by autolysis. He also believes that the alkaline, etherized extracts may prove of therapeutic value when the method of extraction has been perfected because of their selective action on heart and blood vessels.

*Glandular extracts*

*Parathyroid extract* In their late reports on the parathyroid hormone Collip and Clark (201) say that they find that, in uniformity with most other tissue extracts, the intravenous injection of purified parathyroid extract causes a slight fall in blood pressure. The fall is not of long duration and the pressure rather quickly regains its normal level. The subcutaneous injections of the same extract, unless very massive doses are used, have little or no immediate effect on blood pressure. There is apparently some diminution of the blood volume. Major and Buikstra (202) used both Hanson's and Collip's parathyroid extracts. In five control experiments, 5 to 10 cc of extract, injected intravenously into dogs, had no effect upon the normal blood pressure. In dogs to which guanidin had previously been given, parathyroid extract was injected five minutes after the elevation in pressure had ensued. In all of the experiments such injection of parathyroid caused a prompt fall in the blood pressure.

*Insulin and blood pressure.* There has been some discussion recently as to whether the injection of insulin tends to lower blood pressure directly. Weinberger and Holzman (203) discuss this possible hypotensive effect of insulin. Should it be demonstrated that insulin does lower blood pressure, they ask whether insulin, representing the internal secretion of the pancreas does not act in conformity with the hypothesis of an antagonistic action between the hormones of the pancreas and the adrenals. They argue that the height of the blood pressure bears some relationship to the concentration, in the circulating blood, of the adrenal hormone. The administration of insulin should thus tend to lower blood pressure, the fall occurring more readily in conditions where there is hypofunction of the adrenals. McLeod (204) has pointed out that when, in man, the blood sugar decreases to about 0.075 per cent, the patient experiences extreme hunger and a sense of fatigue. He usually becomes anxious and may lose his emotional control. Actual tremor of the musculature is rarely seen, but there is a definite sense of tremulousness, and some incoordination for fine movements.

Vasomotor phenomena are common such as pallor or flushing, sometimes both in succession, a sense of heat or of chilliness, almost

always there is a profuse sweat. At lower levels of blood sugar acute mental distress, mental disturbances, delirium and finally coma, supervene. In explanation of such manifestations, it appears (205) that the stimulus set up by the decrease of the circulating blood sugar may act on certain nerve centers, notably in the region of the pons and medulla. It may be that failure of oxidative processes in the nerve cells is the immediate cause of the symptoms produced. With reference to the asthenia, the study of the cardiac musculature under such conditions becomes of importance. Attention is called to the fact that a suitably perfused heart can function for some time at the expense of its own stores of energy. Locke and Rosenheim had demonstrated long ago that if glucose be added to the oxygen-carrying perfusion solution, a beneficial and sustaining effect is produced on the heart. More recently Hepburn and Latchford (206) have shown that there is a pronounced increase in the sugar utilization of the isolated heart when insulin is added to the perfusion fluid. It thus appears that the heart's utilization of carbohydrate is greatly augmented by insulin. What will be the result of a reduction in carbohydrate supply to the heart *in situ* in the body, such as would be induced by overdosage with insulin? Edwards, Page and Brown (207) have attempted to answer this question by the study of the circulation of animals in a condition of hypoglycemia produced by large doses of insulin. They found little primary change in the peripheral vessels accompanying the hypoglycemia. Under such conditions, however, the heart seems to show a lessening of its dynamic power. This has been shown by electrocardiographic studies, and also by records of intraventricular pressure.

There is a lengthening of the phase of developing tension and a marked decrease in the maximum pressure developed during systole. Some restoration of ventricular power seems to be brought about by the injection of glucose. Such studies as these suggest at least the possibility that the hypotension which seems to follow the administration of large doses of insulin, may act upon the cardiac factor in the maintenance of normal blood pressure. The reduction in the amount of carbohydrate available for and utilizable by the heart muscle may so reduce its power that the asthenic picture supervenes.

*Epinephrin* The intravenous injection of epinephrin produces a

marked rise in blood pressure, which is, for the most part, due to constriction of the vessels of the abdominal cavity. In addition there is some direct action on the heart. Systolic output is increased for a short time. The diminished pulse rate is the result of vagus stimulation. This is, however, often preceded by a period of increased heart rate. After moderate quantities of epinephrin are injected, the blood pressure falls in about five minutes, sometimes sinking below the normal level. Where the blood pressure before injection is very high, a fall of pressure, instead of a rise, may follow the injection. This is due to the fact that epinephrin affects not only the vasoconstriction mechanism, but also the vasodilator. The stimulation of the latter dilates the vessels and reduces the blood pressure. As a general rule, however, the constrictor nerves are so much more powerful than the dilator that the simultaneous stimulation of the latter fails to appear. The variations in the pulse rate after epinephrin may be explained on the basis of the antagonistic action of the terminations of the accelerator nerves in the heart muscle, stimulated by epinephrin, on the one hand, and the effect of vagal stimulation on the other. With exhaustion of the vagal center, the accelerator stimulation again gains the upper hand and the pulse rate is again increased. Summed up, it may be said that the effect of epinephrin on the mammalian heart, in small doses, is to accelerate its rate and strengthen the output. In large doses the acceleration may be excessive and impair the heart efficiency, or the acceleration may be temporarily replaced by inhibition, which also reduces the output. On the bronchial musculature the injection of epinephrin has a marked effect. The bronchi are widely dilated, such action being due to the stimulation of the bronchial sympathetic fibres by the epinephrin, which causes relaxation of the bronchial muscle. All organs containing unstriated muscle are affected by epinephrin. Some undergo contraction, some show relaxation corresponding to the effect of stimulation of the fibres of sympathetic supply. Clinically one chief indication for the use of epinephrin is in cases of marked hypotension due to vasomotor depression without cardiac weakness. Its value as a temporary measure in shock and collapse, as in narcosis for instance, is thus explained. Its action is more prompt after intravenous injection, slower but somewhat more

prolonged when given subcutaneously. In addition, it is of course of great value where local constriction of vessels is desired. By its use almost complete bloodlessness of a part may be secured, without alteration of the general blood pressure. This local ischemia has made the use of epinephrin of particular value in surgical procedures, e g, in nasal operations. It is also of value in controlling hemorrhage in operations in general surgery. The local contraction of the vessels lasts very much longer than that induced by intravenous injection. Even dilute solutions cause ischemia lasting from thirty minutes to two hours, depending upon the rapidity with which the epinephrin is absorbed. Its use in certain chronic hypotensive states has already been discussed (see section on Addison's disease).

*Pituitary extract* Intravenous injection of extract of the infundibular portion of the pituitary causes a rather slow rise in blood pressure. The pressure remains elevated for some time. The rise in pressure is smaller and less abrupt than that which follows injection of epinephrin. It is, however, maintained longer. The rise in pressure is due to constriction of the peripheral arterioles. This constrictor action on the vessels may be shown by perfusing them with saline containing pituitary extract, when the venous outflow is at once reduced. All the arterioles examined appear to be constricted when thus perfused. However, in the body they vary in their response, some being narrowed more than others. The renal vessels are even dilated. There is still some discussion as to the manner of production of increased diuresis which follows the injection of pituitary extract. The increase in blood pressure with dilatation of the renal vessels could explain this, but diuresis may occur in some instances without rise of pressure and without dilatation of the vessels. To explain such cases direct stimulation of the renal cells is assumed. This would fit in with the cases where second injection of pituitary extract depressed the circulation rather than stimulated it, and where nevertheless increased diuresis persisted.

The heart is generally slowed by the injection, the force of the cardiac contraction being increased. These effects are due to direct action on the cardiac and arterial musculature. The occasional fall in blood pressure after pituitary injection is probably due to a depressant action on the heart. Once the blood pressure has returned



to its normal height after the injection of pituitary, a second injection is found to have either no effect or a much slighter effect than the first one. The vessel walls have apparently lost their power of response to the active principle. The blood pressure may even fall instead of rising, owing to the presence of depressor substances in the extract. Clinically, pituitary extract is of value in cases in which hypotension is due to loss of splanchnic vascular tone. It is also of value in cases of low blood pressure due to shock or toxemia especially in combination with saline infusion. Its value in stimulating uterine contraction during labor is well known. In the failure of intestinal peristalsis, e.g., in forms of ileus which sometimes follow extrinsic operation, its use has at times been followed by very good results. The diuretic action of pituitrin is not particularly available for clinical use. Its action in lessening the excessive diuresis in diabetes insipidus, while clinically abundantly attested, has not as yet been satisfactorily explained. The long continued use of pituitary extract in certain forms of dyspituitarism has in many instances been followed by marked improvement in the symptoms.

Tode (356) studied the action of pituitrin on pulse rate, blood pressure, urine and blood cells in human beings. Injections were made into patients with various kinds of diseases of the circulatory or of the autonomic nervous system. The pulse rate was generally lowered. A reverse effect was found at times in patients with cardiac disease or in very nervous persons. Both systolic and diastolic pressures were raised by pituitrin, the latter more than the former so that pulse pressure was diminished. In some cases the systolic pressure fell while the diastolic pressure was raised. In patients who tended to react to pituitrin with marked decrease of pulse rate, epinephrin caused extreme tachycardia. As regards the effect on the blood pressure, it was noted that persons sensitive to pituitrin were not sensitive to epinephrin, and vice versa. Such a relationship was not found to exist between pituitrin and atropin or pilocarpin. Pituitrin injection is therefore not of much value as a functional test of the autonomic nervous system. In some cases injection of pituitrin provoked albuminuria and glycosuria. Blood counts showed increase in percentage of polymorphonuclears and a decrease of lymphocytes, after injection, with diminution of eosinophiles. In half the patients

the changed proportions of polymorphonuclears and lymphocytes did not persist more than an hour after injection

*Thyroid extract* Injected intravenously, thyroid extract produces a fall of blood pressure, as do the extracts of most tissues and organs. The active principle of the iodine compound of the thyroid has been isolated by Kendall and has been given the name thyroxine. In one of his early reports Kendall (209) found that when injected subcutaneously into animals there is at first no effect on either pulse rate or blood pressure. After 24 to 36 hours the animal appears restless and there is a marked increase in pulse rate. If a series of injections be given on successive days, the symptoms are aggravated and there is tremor, loss of weight, and severe diarrhoea. On the fourth or fifth day of injection the pulse rate is between 200 and 300. Later studies were made on animals and on man. Kendall (210) reports that this further investigation has confirmed the earlier finding of delay in the action of thyroxine in animals and also in man, both in the normal condition and in myxedema. It was also found that, although the intravenous injection of thyroxine produces no change in blood pressure, pulse rate, nervous manifestations, or any of the so-called hyperthyroid symptoms, the long continued presence of thyroxine within the tissues of the body produces the picture of hyperthyroidism in its entirety, terminating in great emaciation and eventually in death. One factor, therefore, which would determine the reactivity of thyroxine would be the speed with which the tissues absorb it from the blood stream. It has also been shown that there is a direct quantitative relation between thyroxine and the basal metabolic rate. From this finding is deduced the hypothesis that, without the presence of thyroxine in the body, rapid and large fluctuations in energy output would be impossible. The myxedematous patient cannot carry out much muscular activity, his range of energy output is limited.

Kendall also showed that the increase in pulse rate observed after several injections of thyroxine became more marked if protein food were taken. An association between the thyroid hormone and the amino acids is thus suggested. The fact of the greatly increased effects of the injections of small doses of thyroxine over a prolonged period, rather than a much larger dose at one time, is explained on

the hypothesis that thyroxine acts in the body as a catalyst. It hastens certain metabolic processes which are responsible for the symptoms. When more than the normal amount of thyroxine is administered to the animal organism, there is a distinct lag in the absorption of the compound by the tissues. There is rapid return to normal content if the administration is stopped. No new chemical reactions are brought into play by the administration of thyroxine. As a catalyst, it merely increases the rate at which the fundamental reactions are carried out. The thyroid apparatus has apparently been added to the animal organism in order to permit a greater range of flexibility of energy output than would exist without such a mechanism.

*Extracts of the reproductive organs* Despite the fact that ovarian extract has been in clinical use for thirty years, it cannot be claimed that ovarian organotherapy rests upon a scientific basis even now. In a discussion of the physiology of the mammalian ovary Carlson (211) asserts that there is no reliable evidence that ovarian extract effects are specific for the ovary. Thus it has not been conclusively shown that in spayed females these extracts prevent atrophy of the uterus and maintain estrual periods typical for the species. The reason for past failures may be inherent in the complexity of the ovarian hormones. Certain it is that the ovarian field can point to no such persistent and systematic work of hormone isolation as we have in the case of the thyroid or the pancreas. The sex life of the mammalian female is developed and maintained by the ovaries through continuous and temporary hormone mechanism. Hormones acting more or less continuously develop and maintain the secondary sex organs and act to increase basal metabolism. Temporary hormones from ripe follicles and corpus luteum initiate the estrual cycle, the early interaction between the fertilized ovum and the uterine mucosa, mammary gland hyperplasia, and suppression of follicular growth. Menstruation appears to be only indirectly dependent on the follicular and luteal hormones. <sup>211</sup> follows failure of fertilization and atrophy of corpus luteum. <sup>212</sup> But the hormones initiating menstruation are necessary for menstruation. The initial estrual disorder is due to the ovaries and hence is corrected by ovarian extract.

hormones has so far been isolated, as determined by reliable biological or chemical tests

It is still an open question whether, in experimental animals, any of the ovarian functions can be maintained by substitution therapy, that is by feeding or injection of ovarian extracts. In a critical appraisal of ovarian therapy Novak (212) points out that whatever the relationship of the ovaries to the rest of the endocrine chain may be, they are universally accepted as the organs which are directly responsible for the occurrence of menstruation. Their removal is often followed by certain vasomotor and metabolic disturbances quite similar to those observed at the normal menopause. Certain specific effects of the administration or injection of ovarian extracts have been noted. Some of these may have some bearing on the therapeutic use of these substances. Thus Gonalous (213) found that immediately following the injection of 20 cc of maceration or decoction of gravid corpus luteum, there is a marked fall in blood pressure, amounting to 50, 60 or even 80 mm Hg. The pressure falls rather rapidly, cardiac pulsations are generally weakened and at times in the first few moments after administration, there are deep convulsive respirations. After a few moments the heart's action becomes stronger and the blood pressure rises. The same results, though less marked in degree, were obtained with maceration or decoction of the ovary. These results have however not been uniformly confirmed by other investigators.

Clinically, Novak is inclined to believe that ovarian extracts are of value for the relief of menopausal vasomotor symptoms, but he calls attention to the necessity of extreme caution in attempting to evaluate the rôle of ovarian extracts in the relief of these symptoms. And this largely because these symptoms are purely subjective. They vary greatly as to intensity and duration. He makes no mention of the relief of post menopause hypertension by the use of ovarian extracts. He believes that ovarian extract therapy will succeed when biological chemists can produce ovarian extracts which will really approximate in their effects the action of the ovarian secretion *intra vitam*.

Zenope (214) made a systematic study of the arterial tension, from the standpoint of the endocrine glands, in about one hundred patients. He was struck by an apparent relation between arterial tension and

the ovaries and testes In men, the tension varies inversely with sexual potency, in women with the quantity of menstrual flow Whenever the periods begin to diminish, as at the menopause the blood pressure begins to rise The author favors the view that the hypertension is the result of the hypogonadism and explains the occurrence as due to hyperthyroidism produced by hypogonadism Discussing hypertension after oophorectomy, Cotte (215) finds that removal of the ovaries is likely to raise the blood pressure of the subject afterwards This was true in 36 of 52 women In women showing slight hypertension before operation, there is apt to be a rise still further after operation So also in fibromatous cases In young women conservation of one ovary tends to check hypertension Sterilization by radium does not cause elevation of blood pressure It is variously stated that in post menopause hypertension the diastolic pressure does not rise proportionately to the systolic, so that the pulse pressure is increased The increased blood pressure is not constant There are apt to be periods of remission Culbertson (216) believes that administration of corpus luteum extract reduces post menopause hypertension and brings about a cessation of the vasomotor instability

Wheelon (217) found that extirpation of the testes is followed by a fall of blood pressure, and Wheelon and Shipley (218) found that the presence of successful testicular grafts in any part of the body would reestablish normal vasomotor tone

#### THE EFFECTS OF CERTAIN DRUGS ON BLOOD PRESSURE

##### *The nitrite group*

Different members of the nitrite group have an action on the circulation which is essentially similar The variations in effect are those of promptness, intensity and duration of action They lower blood pressure by their action on the arteries, which they cause to dilate by depressing the muscle of the arterial wall The heart rate is increased, so that the heart itself is not responsible for the change Both arterioles and veins widen considerably under the action of the drugs The vessels of the abdominal organs and the face are more affected than those of the extremities The vasomotor center is not

concerned in the widening of the vessels, for if, for instance, amyl nitrite is allowed to pass through the medulla without reaching the peripheral vessels, no fall in pressure occurs. Also, stimulation of a constrictor nerve, such as the splanchnic, still produces some rise in pressure, showing that the nerve terminations are still intact. Tolerance to the nitrites is often quickly established. It is also true that the effects of different members of the group may vary in their effect in a given individual. Amyl nitrite, when inhaled, acts very promptly, but the effect is not of long duration. Sodium nitrite is administered by mouth. It acts much more slowly than amyl nitrite, but the effects last longer. Nitroglycerin, given either by mouth or by hypodermic injection, acts more powerfully than either the metallic or the alkyl nitrites. Its action commences rather promptly after administration, and lasts much longer than does that of amyl nitrite. Erythrol tetranitrite and mannitol hexanitrate act more slowly than other members of the group, but the effects persist longer. The employment of the nitrites in hypertension is to be classed as purely symptomatic medication. They are essentially emergency drugs. They are of value in cases of threatened apoplexy or cardiac failure from hypertension. After intracerebral vascular rupture has occurred they are contraindicated. So also in marked arterial hypotension. They should not be used as primary cardiac stimulants in the hypotension of acute febrile disease or in shock.

Voegtlin and Macht (219) found that certain of the glucosides of digitalis produced contraction, while the nitrites produce dilatation of the coronary arteries. They believe therefore that the combination of a nitrite with digitalis is of particular value in the treatment of angina pectoris.

Cornwall (220) summarizes the indications and contraindications for the nitrites as follows. The general indications for their use are

- 1 To relieve symptoms of localized arteriosclerosis or arterial spasm in vitally important regions of the body
- 2 Also when there is pain due to contracted or diseased arteries in other regions
- 3 To reduce hypertension in selected cases if its continuance threatens accident to the cardiovascular apparatus. The chief contraindications for the nitrites are hypotension, advanced chronic

nephritis with hypertension, or hypertension due to severe toxemia, and finally individual idiosyncrasy to the drug group.

### *Alcohol*

There is much difference of opinion as to the effects of alcohol on the circulation. Such differences have arisen as the result of both clinical and experimental studies. The pulse is accelerated during the excitement of alcoholic intoxication, but this is not due to any direct action on the heart. The flushing of the skin which occurs in alcoholic intoxication indicates dilation of the skin vessels. Indeed it seems to be fairly well determined that one chief effect of alcohol on the circulation is vasodilation. Very large quantities of alcohol cause a marked fall in blood pressure through weakening of the vasoconstrictor centers and the heart muscle. However, the quantities of alcohol required to produce any marked drop in blood pressure are far in excess of those used therapeutically. Alcohol produces a definitely unstable vascular tonus. Both clinical and experimental evidence has been adduced to show that alcohol is not advisable as a stimulant in conditions of low blood pressure. In the vascular failure of the acute infections and in surgical shock it may be actually harmful.

### *Iodides*

Iodides are certainly not vasodilators in the sense that the nitrites are. Where existing hypertension is lowered after the prolonged use of iodides, the inference is that the hypertension was due to luetic aortitis or endarteritis. Cushny says that the supposed pressure lowering effect of the iodides in arteriosclerosis has been ascribed to their power of lessening the viscosity of the blood. He adds that the experimental evidence on which this explanation is based is not at all conclusive. It seems safe to say that the iodides have no direct effect upon blood pressure.

### *Chloral*

In therapeutic doses chloral has comparatively little effect on the circulation. The heart is somewhat slowed in its action and there may be some flushing of the face and head from some obscure central

action In poisoning with chloral the blood pressure is reduced by weakness of the vasomotor center and of the heart The action on the heart in chloral poisoning resembles that of chloroform The auricles are affected sooner than the ventricles and the strength of contraction fails while the heart rate is increased Drugs of the chloral group should not be used to reduce blood pressure By relieving pain and nervous tension, and promoting sleep, they may be of indirect value in certain benign types of hypertension

### *Opium*

The effect of opium on the circulation itself is not marked The blood pressure does not change The peripheral vessels in general show no change in calibre, with the exception of those of the skin, especially of the face and neck The fall in pressure which follows its use in certain cases of angina pectoris and hypertension from broken compensation is due to its sedative effect on the nervous system and its stimulation of the vagus, which, by slowing the pulse, tends to lower the blood pressure somewhat Morphine itself tends to dilate the coronaries which may be another reason why the drug is so valuable in angina pectoris Macht (221) has called attention to the fact that the combination of caffeine and papaverin is particularly effective in causing dilatation of the coronaries Macht (222) has also found that papaverin, in addition to its analgesic effect, produces some slowing of the cardiac rate and increases myocardial tonicity It tends to produce a fall in blood pressure from peripheral action on the vascular walls The value of morphine and papaverin in angina pectoris or in cases of arterial hypertension where an analgesic sedative is required, has been attested by abundant clinical experience It used to be held that the use of opium or its alkaloids was contra-indicated in the presence of nephritis It is probable that the supposed danger attending the administration of opium in some form in such cases has been greatly exaggerated In certain types of cardio-vascular-renal disease with marked hypertension, opium in some form is nearly always of value, at times an almost indispensable aid to treatment



*Watermelon seed*

Recently Barksdale (223) has been studying the pharmacologic effects of the seeds of the watermelon (*Cucurbita citrullus*). To this active principle the name of cucurbocitrin has been given. When either the crude extract or the active principle was given orally, the outstanding effect was a prompt lowering of blood pressure by capillary dilatation. The diminution of peripheral resistance thus brought about, relieved the heart of part of its load. Necropsies on rabbits following lethal doses showed congestion and hemorrhages of lungs, liver and kidneys. Also, there was marked dilatation of the bladder wall, with coincident increased mucus secretion on the bladder wall, suggestive of selective action of the drug. Clinically, in man, in cases of moderate hypertension, the administration of the extract was followed by a drop in both systolic and diastolic pressures. Subjectively, the patients felt better after the administration, and some of them were able to tell when the pressure was rising after the drug had been withheld for a few days. The toxicity of the drug is extremely low. No ill effects were noted in any case. The drug's action is rather slow, but prolonged. In four cases of acute cystitis, the clinical relief was very prompt. In cases of marked arteriosclerosis, the drug had less effect. Barksdale suggests the usefulness of the drug in cardiorenal hypertensive conditions, and believes that it will prove of value in certain acute and chronic inflammations of the urinary bladder.

*Glucose*

Of late there have been some studies on the effect of the intravenous injection of glucose into the circulation. Meyer (224) used intravenous injections of 10 to 20 cc. of a 10 to 20 per cent solution of glucose in several hundred patients with hypertension. It was found to enhance the action of simultaneously injected digitalis and strophanthin. It seemed to prevent the onset of attacks of angina pectoris which sometimes follow the injections of strophanthin. He had excellent results in angina pectoris by the injection of glucose every day or every other day. At times he combined glucose with theophyllin. The blood pressure became permanently lower in many cases. He recommends the treatment even in diabetics.

with angina pectoris Wichels (225) also secured lowering of the blood pressure in twenty-one of twenty-six cases of genuine hypertension after intravenous injection of small amounts of glucose. The action of levulose and of sodium chloride was less pronounced. He also confirmed the finding of decreased tonus of surviving strips of intestine from guinea-pigs, cats and dogs after addition of 0.1 per cent glucose, if their tonus had been increased by the addition of serum to the fluid in which they were suspended. The glucose had no influence on strips which were not under the action of the serum. He concludes that the glucose acts by changing the colloidal condition of the serum. Weil (226) studied the capillaries after intravenous injection of small amounts of glucose. In patients with hypertension he found a widening of the previously narrow lumen of the capillaries and an improved capillary circulation, which paralleled the lowered blood pressure. In most of the cases of advanced nephritis, such changes were not observed.

(The effect of glucose on the circulation is also discussed in the section on action of insulin.)

#### *Quinidin sulphate*

With the advent of quinidin sulphate as a cardiant of value in the management of certain types of myocardial degenerations, particularly of auricular fibrillation, experimental studies of the pharmacological action of the drug were made by various observers. Jackson, Friedlander, and Lawrence (228) made studies of the action of quinidin on normal animals. The immediate result of the intravenous injection of the drug was found to be a marked drop in blood pressure. It was found that after the administration of quinidin the animal was very much less sensitive to the action of epinephrin than it had been before such administration. It was concluded that large doses of quinidin depress the vascular sympathetic nerve endings. It was also shown that there was definite dilatation of the peripheral vessels, and it was concluded that quinidin acts primarily on the peripheral vessels, possibly to a considerable extent on the capillaries. The authors suggested that a study of the peripheral circulation be made in patients to whom the drug is given, both before and after administration. It was believed that such investigations might throw

considerable light on the question of the proper selection of cases for quinidin treatment. Clinical experience had shown that the therapeutic effects of the drug varied greatly in different individuals.

So far as pulmonary pressure was concerned, it was found that small doses tended to produce a primary rise in the pulmonary pressure, whereas large doses produced a fall out of proportion to the drop in systemic pressure. This was believed to be due to dilatation of the pulmonary arterioles and capillaries under the action of quinidin. The authors stressed the action of the drug on the peripheral circulation, by causing vasodilation. Also it was shown that so far as the heart muscle itself is concerned there was a primary reduction in heart volume. Recently Gordon, Matlin and Levine (229) have made detailed studies of the action of quinidin on normal animals. Immediately following non lethal doses of quinidin there was a striking fall of blood pressure, beginning a few seconds after intravenous injection. The effect on respiration was directly proportional to the size of dose used. The heart continued to beat after complete respiratory failure had occurred, for as long as two minutes. Roentgenograms taken at frequent intervals during the fall of blood pressure after the injection of large doses of quinidin, showed at first a slight contraction of heart volume, followed by dilatation. With small doses there followed the contraction *without* dilatation. Marked dilatation always occurred as a terminal event. These authors also stress the points, mentioned above, that in addition to the action on the heart muscle, quinidin has a marked effect on the abdominal and peripheral vessels. The blood pressure lowering effect is doubtless largely due to this factor.

#### *Mistletoe (Viscum album)*

In Europe, mistletoe has been used rather extensively for the purpose of lowering blood pressure. In a recent study of its action Bijlsma (230) found that it reduces pressure by dilatation of the blood vessels, without action on the centers in the medulla. The pulse is slowed because of irritation of the vagus.

#### *Salvarsan*

In animals the intravenous injection of salvarsan causes a marked fall in blood pressure. This probably arises in part from direct

action upon the walls of the arterioles and capillaries, in part from central action. Other observers regard the action as due to direct weakening of the heart muscle. The action of neosalvarsan is less marked than that of salvarsan. Pomaret (231) has found, in experimental work on dogs, that the phenomena of shock under intravenous administration are phenolic shocks, resembling the picture as seen after intravenous injection of more simple phenol compounds (trinitrophenol and carbolic acid). The degree of shock produced was in direct proportion to the degree of acidity of the injected fluid and thus to the degree of flocculation of the blood plasma produced. Intramuscular injections in dogs do not produce these shock-like states. In man the degree of blood pressure reduction produced by the injection of neosalvarsan is never sufficiently great to endanger a normal circulatory mechanism. Wherever, however, marked hypotension exists from any cause, the injection of arsphenamins may have serious consequences. Clinical experience has also shown that, in the presence of severe cardiovascular lesions, in severe nephritis and diabetes, in very old or very feeble persons with malnutrition and emaciation, the organic arsenic preparations must be given with extreme caution and in reduced dosage.

Occasionally certain drugs exert marked vasomotor depressive effects in susceptible individuals. Scully (232) has recently reported a case of such idiosyncrasy to cinchophen.

### *Cinchophen*

Toxic symptoms have been reported after the administration of cinchophen by various observers. Skin eruptions are not uncommon. The marked vasomotor depression observed in this case is quite unusual. The patient, male, age 48, had an arthritis of the hand joints. Blood pressure 120/78. Pulse regular, 80, heart sounds clear. He was given one dose of cinchophen (0.5 gram). Three hours thereafter he had a chill, the skin became pale and the heart began to beat forcibly, heart rate 120. Blood pressure fell to 65/42. After the administration of aromatic spirits of ammonia and strychnin, the pressure rose to 80/44. An hour later it was 108/72. It was then found that the patient had had a similar attack after a single dose of cinchophen, two years before. Scully feels that the

combination of rapid, weak pulse with hypotension with good heart action indicates a marked vasomotor depression rather than a cardiac phenomenon

### *Bismuth subnitrate*

Frick (233) in discussing the use of bismuth subnitrate in peptic ulcer reports three cases of nitrate intoxication due to large doses of bismuth subnitrate. The symptoms were cyanosis, asthenia and marked hypotension. He adds that there is no danger of nitrate intoxication, even with very large doses of bismuth subnitrate, provided thorough evacuation of the bowels is secured. The three patients reported were well twenty-four hours after thorough catharsis.

### *Digitalis*

A critical review of the experimental and clinical studies on the relation of digitalis to blood pressure has been made by Robinson (227).<sup>1</sup> In 1902 Gottlieb and Magnus showed that digitalis bodies are capable of producing marked vascular constriction through direct action on vessel walls. By the use of doses of various digitalis bodies which were five to fifteen times the minimum lethal dose, they produced striking elevation of blood pressure in experimental animals. This was caused in part by constriction of the splanchnic vessels, by direct action of the drug upon their walls. Eggleston, studying the investigations of the Gottlieb school, commented on the fact that these studies were made on experimental animals with doses proportionately much larger than those which are employed therapeutically in man. The discovery that elevation of blood pressure is not a constant or conspicuous effect of digitalis in man came with the era of the widespread use of the sphygmomanometer. Accurate objective observations then began to replace deductions made from animal experiments, and observations strongly influenced by preconceived ideas. Eggleston summarized the blood pressure findings in 181 cases after digitalis medication. These findings were made by various observers. In 66 of the 181 cases (about 36 per cent) the blood pressure rose, in 57 (31 per cent) it fell, in 58 (32 per cent) it did not change.

<sup>1</sup> Detailed bibliography appended

In 116 cases where the diastolic pressure was studied, it rose in 24 (15 per cent) and fell in 76 (65 per cent) The systolic pressure in this series showed no constant change, the diastolic pressure was apt to fall There was general agreement that digitalis has very little effect on the systolic pressure when used therapeutically It was even suggested that it actually causes some vasodilation which would account for the reductions in diastolic pressure

Eggleston made careful studies of the effect of digitalis on the blood pressure of fourteen patients, six of whom had high initial pressure, while eight had normal or low initial pressure He found that the administration of large doses of digitalis had very little tendency to raise the systolic pressure *Per contra*, the diastolic pressure was markedly lowered in 50 per cent of the cases studied Robinson emphasizes the fact that hypertension does not contraindicate the use of digitalis Indeed hypertension may, at times, be advantageously affected by digitalis action Windle has recently found that digitalis is valuable to patients with degenerated arteries, hypertension and anginal symptoms It may even bring about immunity from anginal attacks During a study of one hundred patients some of whom had hypertension, to whom very large single doses of tincture of digitalis were given, Robinson noted that the systolic pressure tended to approach more nearly the normal level after the drug was given In other words, elevated blood pressure fell, while abnormally low pressure rose Recent carefully controlled clinical studies have thus shown that arterial hypertension must not be accepted, *per se*, as a reason for withholding digitalis when it is otherwise indicated With reference to the action of digitalis on the coronary circulation, there is at the present time no evidence to prove that digitalis causes coronary constriction The experimental work of Meyer, Sakai and Sanjoshi have shown that the coronaries do not contract under the influence of digitalis If they are affected at all, they probably dilate The suggestion of Voegtlin and Macht as to the advisability of combining nitrites with digitalis in the treatment of angina pectoris has already been alluded to (See section on action of Nitrites)

## PRESSOR DRUGS

Certain drugs have been used at times for their blood pressure raising effects. Such effects are naturally for the most part ephemeral. For the treatment of such conditions as essential hypotension (qv), various drugs have been recommended. A discussion of the action of some of the so-called pressure drugs follows.

*Ephedrin*

Ephedrin is the name given to an active principle of an Asiatic drug, Ma Huang (*Ephedra vulgaris* var *helvetica*). This drug has been used in medical practice in China for more than five thousand years. Ephedrin has physiological effects which are very similar to those of epinephrin and tyramin. Recently studies have been made of the pharmacologic effects of this drug. Miller (234) finds that ephedrin has distinct practical advantages over epinephrin because of its more prolonged action and because it can be administered effectively by mouth. In doses of 50 to 125 mgm given orally or subcutaneously, ephedrin sulphate usually raises the systolic and diastolic blood pressure, and decreases the pulse rate for a period of several hours. It also stimulates the heart action and has a tendency to increase urinary output. It sometimes increases the basal metabolism. Its administration caused temporary improvement in two cases of Addison's disease, and gave relief in the paroxysmal attacks of some cases of asthma. It relieved the subjective sensation in a case of urticaria, and caused disappearance of the urticarial wheals in a case of serum sickness. It produced marked temporary improvement in a case of circulatory failure incident to myocardial disease. In one case of complete heart block it produced an increase in both the auricular and ventricular rates and caused alterations in the electrocardiogram. Locally applied to the nasal mucus membrane it causes prompt vascular contraction lasting more than three hours and occurring without local irritant effect. It is believed that a wide range of usefulness of ephedrin will be found in the treatment of acute circulatory depression, of asthma, and in the management of certain congestive nasal conditions. Chen (235) finds that ephedrin acts through peripheral stimulation of the sympathetic nervous system.

It raises blood pressure in hemorrhage and in experimental shock induced by histamin, peptone, anaphylaxis, or surgical manipulation. The rise in blood pressure is permanent under favorable conditions and this effect of the drug is due to increased cardiac output and not to arterial constriction. Ephedrin fails to act when the heart beat becomes impaired, or respiration ceases, when the degree of shock is too extensive or when hemorrhage exceeds 25 per cent. It has, however, no harmful effects. Chen and Schmidt (236) report that the toxicity of ephedrin is very low. It is effectively absorbed from the intestinal tract. It is being tried out in Addison's disease, apparently with good effects. Results in shock and acute circulatory depression have been good. The drug also acts as a mydriatic. Average dosage has been 40 to 60 mgm given by mouth or intramuscularly.

### *Caffeine*

In doses ordinarily used in man, there is not much change in blood pressure as a rule. Such increase in pressure as is found is probably due to increased splanchnic tonus. In cardiac inefficiency caffeine may even cause a drop in blood pressure. This may perhaps occur indirectly, on account of the diuresis induced by the caffeine which reduces the blood volume. Caffeine has a direct dilator effect on the coronaries. This will explain the reported value of its use in angina, particularly in combination with such drugs as papaverine. (See section on action of opium.)

### *Strychnin*

The heart is not directly affected by strychnin in mammals, though its action may sometimes be slowed by stimulation of the inhibiting center. The vasomotor center is, however, directly stimulated by ordinary therapeutic doses of strychnin. It is on this basis that there is justification for the use of strychnin in conditions of low blood pressure, associated with marked depression of the vasomotor center. The good effects reported from the use of strychnin in essential hypotension, for instance, are probably due to the stimulation of the brain and spinal cord produced by the drug, and not to any direct effect upon the circulatory mechanism. Crile was unable to find that



strychnin was of any value in the hypotension of shock Cabot could not find any change in blood pressure after its use in a number of conditions in which it is ordinarily advised It does seem to be of value in helping such forms of circulatory weakness as are due to inefficiency of the vasomotor center Its supposed value has probably been greatly overestimated by clinicians

### *Atropin*

Atropin increases the pulse rate by depression of the peripheral ends of the vagus The blood pressure often falls for a few minutes at first, as the result of a direct action of the drug on the heart muscle It then rises above the former level, as a result of cardiac acceleration, when this is marked The rise from the acceleration is not marked unless there should happen to have been unusual activity of the inhibiting mechanism previously There is no evidence that the vasoconstrictor center in the medulla is excited by atropin Concentrated solutions of atropin perfused through the vessels cause them to dilate from action on their walls, however, there is no evidence to show that this occurs in the living animal Clinically the pressor effects of atropin are not marked It is however a valuable remedy in the wet clammy stage of vascular collapse Combined with morphin it is of much value in the treatment of pulmonary edema

### *Ammonium*

Ammonium, in the form of aromatic spirits, acts promptly as a cardiac stimulant, though its effect is very temporary After its exhibition the blood pressure rises due to constriction of the peripheral arterioles, induced by stimulation of the vasomotor center At times the heart is slowed owing to increased activity of the inhibitory center Ammonia is thus valuable in transient cardiac and vasomotor weakness It is also very useful in the relief of gaseous gastric distension in arteriosclerotic cases associated with precordial distress.

### *Camphor*

Camphor is said to raise blood pressure by medullary and cardiac stimulation After its use there is a transient rise in blood pressure

This may be succeeded by a fall, due to dilatation of the peripheral vessels through direct action on their walls. Where very large doses of camphor are given, great variations in blood pressure may occur. Such variations appear to arise from a direct action on the vasomotor center, which partakes in the general stimulation. In the light of recent studies it appears to be established that definite results on the circulation can only be obtained by the use of very large doses, and with such doses the possibility of toxic effects must always be borne in mind.

### *Ergot*

Cushny calls attention to the fact that the action of ergot in the living organism has been elucidated by the experimental studies of Dale. It is due to the action of its bases, ergotoxin, tyramin, and ergamin. The first two of these resemble epinephrin in some of their effects, though the ergotoxin is probably of much more importance in the action of ergot than tyramin. Injected intravenously, ergotoxin causes an abrupt rise in blood pressure due to its action on the peripheral vessels. There is constriction of the abdominal vessels, and of the vessels of the extremities. The heart action is often accelerated at first and then slowed. This is due partly to vagus stimulation, partly to direct action on the heart muscle. Sometimes the slowing of the heart may be so marked as actually to lower the blood pressure. Ergamin produces varying effects on the vessels in different animals. Thus, in the dog and cat, it causes a profound fall in blood pressure from dilatation of the peripheral vessels. In the rabbit, on the other hand, the peripheral vessels are constricted by it.

Clinically the effect of ergot on the blood pressure varies according to the relative amounts of the bases present. The heart is not acted upon as strongly as the vessels by the ergot bases. Clinically ergot is of comparatively little value as a means to restore vasomotor tone, because its effects are very transitory, though its value as a stimulator of uterine contraction is undisputed. The necessity for insisting upon physiological standardization of preparations for clinical use can be appreciated from a consideration of the variations in base content of different varieties of the drug.

## ESSENTIAL HYPOTENSION

Various authors have called attention to a syndrome whose chief objective finding is marked hypotension. Physical examination in these cases shows no organic lesion. The subjects complain of headache, vertigo, and palpitation after moderate exertion. There is marked fatigability, mental and physical. The patients lack stamina, have cold, clammy extremities and complain of their inability to perform the daily routine of their lives. The appetite is capricious and dyspeptic symptoms of various kinds are common. Constipation is found in some cases, but by no means in all. The patients are, as a rule, neither neurasthenic nor psychasthenic, and the cases cannot be classed under the psychoneuroses. The condition is most commonly found between the ages of 20 and 40. Lawrence (248) has reported a series of 20 cases. All were between 15 and 35 years of age. Only one was under 20 years. There were 14 females and 6 males. Physical examination was negative, except for marked hypotension in each instance. There was no anemia, no evidence of focal infection, sleep was poor and there was marked fatigue on arising. The patients usually improved toward afternoon of each day. They usually felt best after meals, at which time the pressure were also highest. Lawrence emphasizes the fact that the condition is probably often wrongly classed as neurasthenia. In five of the cases the use of atropin was followed by marked improvement. He points out that a true hypoadrenia may occur in diseases of the adrenals, without the picture of Addison's disease. He thinks that essential hypotension may occur without organic disease, after prolonged mental or physical strain, and that the symptom complex here may differ from that of hypoadrenia only in degree. Roberts (249) applies the term "somasthenia" to the condition. He finds that it occurs between the ages of 20 and 40, that it rarely occurs after forty. Women are affected much more often than men. The symptoms in order of frequency are exhaustion, nervousness, headaches, pains in chest, abdomen or extremities, indigestion, constipation, backache, dyspnoea, insomnia and palpitation. The three chief complaints are exhaustion, lack of endurance and headache. Hypotension is constant. The patients are not neurasthenics, and apart from the diagnosis of visceroptosis or mild

focal infections, hypochlorhydria or secondary anemia, no actual pathologic condition can be demonstrated. The cases cannot be classed under the psychoneuroses. Howe (250) believes that the presence of persistent hypotension, in the absence of constitutional anomaly such as status lymphaticus for instance, should always awaken the suspicion of focal infection. Goodman (251) reports cases of so-called hypotension, showing the usual picture. He, too, stresses the fact that the patients are not neurasthenics. He offers no explanation for the hypotension, rejecting so called intestinal autointoxication on account of lack of definite proof of its existence. Barach (252) believes that hypotension is due to respiratory deficit and decreased oxidation. Arterial pressure is dependent, he says, on the energy of the heart, the resistance in the arteries and the quantity and character of the blood. But, he adds, "we will place before these, and as the first factor, 'respiratory effort and oxygenation'" In his series of 100 cases of essential hypotension there were forty males and sixty females. Taken as a group the subjects were undersized, nonathletic. They had narrow nostrils, narrow chests and slender bodies. They belonged to the hyposthenic or asthenic types. They had a chest capacity smaller than normal, were shallow breathers, and showed a marked tendency to muscular drooping. He believes that all of their symptoms were due to want of oxygen. Levison (253) studied the vital capacity in 10 patients with essential hypotension. Eight of them had vital capacities of 85 per cent or over. In four cases complete chemical studies of the blood were made. These did not vary appreciably from normal limits. Levison thinks that the etiology of essential hypotension has to do with constitutionally inferior states, possibly with endocrine disturbances, with post infectious exhaustions or toxemias. Cases where definite cause for the hypotension are to be found are not to be classed as essential. Fossier (254) says that all hypotheses heretofore advanced as to the etiology of essential hypotension have been either "unproved, refuted or impractical." He says that the condition is usually found in asthenics or splancnoptotics. It is rarely if ever found in sthenic or hypersthenic individuals. It is found in persons having an elongation of the ascending aorta and a narrowing of its hemicycle, or in persons where the heart is poorly supported by the

diaphragm He feels that this explanation is in accord with physical laws the longer the pipe, the smaller the radius of the bend, the smaller will be the final velocity energy Or, in man, the longer the ascending aorta, the narrower the diameter of the arch, the heart pressure remaining constant, the lower will be the systolic pressure He adds that subjects belonging to the hypersthenic type are immune from essential hypertension Editorial comment on this statement is made thus "We doubt if this statement will pass unchallenged We ourselves have seen persons of this type with arterial pressures of less than 110 mm Hg with no apparent etiological factor, i e essential hypotension " Believing what he does, it is not surprising to find that Fossier advocates as measures for the relief of essential hypotension, the treatment of the splanchnoptosis by abdominal supports, the strengthening of the abdominal muscles and the increase of abdominal fat Mosenthal (255), in describing the typical syndrome, is unable to decide whether the hypotension is cause or effect He suggests that the hypotension in these cases may be due to the storage of excessive quantities of blood in the splanchnic vessels Greaves (256) in the course of a general discussion of low blood pressure also calls attention to the importance of the splanchnic pool in relation to hypotension The necessary variation in the blood supply of the splanchnic area calls for close control of this supply by the sympathetic nervous system Loss of tone in the sympathetic causes an increased amount of blood to be in the splanchnic area and this causes hypotension

It is thus apparent that the definite etiology of essential hypotension has not been worked out Apparently one underlying factor must be loss of vasomotor tone During acute infections, in the course of chronic infections and as the result of focal infections such loss of vasomotor tone finds a readier explanation For the explanation of the hypotension in the syndrome under discussion, such an explanation does not avail Friedlander (257) has suggested a hypothesis, admittedly not proved as yet, which has both clinical and experimental evidence to support it This may be summarized as a theory of capillary stasis The rôle of capillary stasis in the production of wound shock has already been discussed (See section on Wound Shock.) There is however much evidence to show that in non trau-

matic conditions there may be the possibility of capillary stasis and consequent hypotension, by the giving off of small quantities of histamin or histamin-like bodies which act as capillary poisons. This evidence may be briefly recapitulated here. In 1910 Dale and Laidlaw (258) called attention to the reduction in blood pressure that can be induced by the injection of minute amounts of histamin. Later, attention was called to the shock-like character of the changes that histamin occasions: constriction of the arteries, oligemia, increased ratio of corpuscles to plasma, and failure of output. The arteries and veins contain little blood. The blood is concentrated in the capillary areas. Dale and Richards later showed that the low blood pressure was due to dilatation of the capillaries, pooling of the blood within them, poisoning of the endothelial walls so that they become abnormally permeable. Escape of plasma through these walls into surrounding tissues and consequent concentration of the corpuscles are outstanding features. These observations are of special import in that they suggest that "the action of histamin may reasonably be regarded as typifying the action of a large class of poisonous protein derivatives, products of partial digestion, of bacterial action and of tissue extractives" (Cannon). It is known that histamin is present in the mucosa of the small intestine. Abel and Kubota have recently shown that histamin is perhaps a widely distributed constituent of animal tissues. It is, of course, known that histamin is not the only constituent of tissue extracts capable of lowering blood pressure. Indeed reference has already been made to the fact that the depressor substance in liver extract is probably *not* histamin. (See section on Liver Extract.)

This general view of capillary stasis and its possibilities has been distinctly strengthened by the researches of Krogh (259) on capillary circulation. He points out that "a very essential feature in the etiology of shock is the vicious circle which is set up by the poisoning of the capillaries. When the circulation begins to fail, the blood supply to the tissues suffers, and this in turn leads, by reason of oxygen lack, or by reason of the diminished supply of tonic hormone, to still further dilatation." Later he adds the significant statement that "states of circulatory failure, similar in nature to traumatic shock are, I believe, not at all infrequent." The rôle of capillary poisons in the

production of pathological changes in the circulatory mechanism of the body is thus summed up by Dale (260) in the closing paragraph of the first Herter lecture for 1919

We arrive at the conception of a group of toxemias, some of bacterial, some of traumatic origin, due to toxic substances having the same general action on the capillary circulation which we have been considering in the case of histamin. Whatever further chemical investigation may reveal as to the nature of such substances, and their relation to histamin, I think there can be little doubt that this conception of the capillaries as an actively contractile part of the vascular system, having an intrinsic tone which can be modified either by nervous or chemical influences, is destined in future to play a part of increasing importance in conceptions of the mechanism by which the blood supply to the tissues is regulated under normal physiological conditions, and of the disturbances by which it is rendered pathologically inadequate.

As a working hypothesis, not proved as yet, persistent low pressure, as in cases of so called essential hypotension, may be due to poisoning of the capillaries by histamin or histamin-like bodies. Considerable evidence has been accumulated to justify such a view, though admittedly much work must be done before this hypothesis may be said to rest on the basis of established fact

#### HYPOTENSION DUE TO MALFUNCTION OF THE FACTORS WHICH NORMALLY MAINTAIN BLOOD PRESSURE

##### *The first factor, The cardiac factor*

It is difficult to evaluate the rôle that heart lesions play in the production of persistent hypotension. In certain of the acute infectious diseases, as, for example, typhoid fever and pneumonia, it is generally agreed that the weakening of heart power from cloudy swelling or degeneration of the muscle fibres may constitute the most important single factor in the production of the hypotension so commonly seen in these conditions. In chronic heart disease, however, failing circulation may be associated with a normal or even an increased blood pressure, owing to compensatory constriction of the peripheral arterioles. This peripheral vasoconstriction, however, necessarily reduces the capillary blood flow. As Wiggers points out,

the inability to increase the capillary flow during exercise is probably primarily responsible for the muscular weakness and fatigue so commonly found with decompensated hearts. As the heart fails more and more, arterial pressures in the central arteries are inadequate to force a sufficient supply through the brain arteries. The resulting cerebral anemia is one of the causes of dyspnoea and leads to fainting or syncope.

In estimating the rôle of the diseased heart as such in the maintenance of blood pressure, several factors have to be taken into consideration. The capacity of the hypertrophied heart to do work has been made the subject of much study. It had been believed that a physiological hypertrophic compensation goes hand in hand with anatomic hypertrophy. It is now quite generally agreed, however, that the reserve power of hypertrophied hearts is never equal to that of normal hearts. Krehl has pointed out that hypertrophied heart muscle is abnormally sensitive to damage. Albrecht has shown that the hypertrophied heart is, from the beginning, a diseased heart, its weakness being due to the commonly associated myocardial degeneration. Such myocardial degeneration being progressive tends to steadily diminish the contractile power of the heart. This, in turn, steadily diminishes the reserve power of the heart. Furthermore, with the advent of the cardiac arrhythmias that are associated with myocardial degeneration, the dynamics of the circulation are so much interfered with, that the reserve power of the heart is still further reduced. It has also been shown that during hypertrophy there is no proportionate increase in the heart's blood supply, so that the capabilities of the anatomically enlarged heart are, *ab initio*, somewhat restricted.

Another factor of importance is the heart rate. The essential cardiodynamics underlying an increase in heart rate have been analyzed by Henderson (262). The more the heart rate increases, the more the period of diastolic filling is cut short and the smaller is the systolic discharge of the beats. Clinical studies have accordingly been made of the product of heart rate and pulse pressure (difference between systolic and diastolic pressure). As Wiggers has pointed out, however, pulse pressure is an index of the volume of cardiac discharge only when it may be assumed that neither the viscosity of



the blood, nor the diameter of the peripheral vessels, nor the cubic increase in volume for definite pressure increments, varies. Too much reliance is therefore not to be placed upon occasional estimations of heart rate-pulse pressure products. Repeated estimations of the product in the same individual over considerable periods of time may however have some prognostic value as to the condition of the myocardium.

As has been pointed out in the discussion of traumatic shock and hemorrhage, direct reduction of the blood volume (oligemia) is a factor of importance in the resulting hypotension. Such oligemia according to careful clinical and experimental study also plays a rôle in the hypotension accompanying certain forms of chronic myocardial disease. So, too, the relaxation of cardiac and arterial musculature as the result of deficient oxidation (relative acidosis) is a factor in cardiac hypotension.

With this necessarily cursory and incomplete introduction, it seems pertinent to discuss the hypotension in various types of cardiac disease in some detail.

*Myocardial degeneration.* Hypotension is *not* common in the early stages of myocardial degeneration, though of course it occurs frequently in the terminal stages. What is much more common is that the systolic pressure is approximately normal while the diastolic pressure is very high (Dock). There is thus a marked diminution in pulse pressure. Speaking in general terms, it may be said that in myocardial disease, the smaller the pulse pressure, the lower the limit of cardiac reserve. Stone (263) believes that progressive narrowing of the pulse pressure is of serious prognostic import in such conditions. Wolferth (264) emphasizes the fact that in myocardial degeneration, *with improvement under treatment*, the systolic pressure may rise, fall or remain stationary. Whatever changes occur tend to be toward the normal level. On the other hand the diastolic pressure in such cases tends to fall coincidentally with the improvement. This of course brings about an increase in pulse pressure.

Acute hypotension occurs not infrequently in subjects with myocardial degeneration who have been hypertensives. Such sudden drops in pressure, are, as a rule, of rather serious prognostic omen, as emphasized by Bishop (265) and Jeanneney and Tanzin (266).

among others. These authors point out that if the blood pressure maintaining power of the heart is lost, such hypotensives are sure to show progressive deterioration in the pressure of the demand for extra circulatory power.

When, as part and parcel of myocardial degeneration, various arrhythmias occur, hypotension is rather frequently seen.

*Tachycardia* Low blood pressure is, as has been shown, generally associated with tachycardia, especially the tachycardia resulting from fever. The hypotension here is due in part at least to reduced cardiac power.

In essential paroxysmal tachycardia there is usually hypotension during the attack. This is due to insufficient filling of the ventricles during diastole. Pal thinks that the drop in pressure during the paroxysm is due partly to insufficient filling of the heart chambers, partly to vascular dilatation. The minute volume flow is thus greatly reduced. The systolic pressure falls without much change in the diastolic pressure, so that pulse pressure is markedly reduced. Where the paroxysmal attacks of tachycardia are of short duration, the hypotension is usually temporary also. Where however the attacks of paroxysmal tachycardia tend to increase in duration and in frequency, the blood pressure level tends to sink permanently.

*Bradycardia* Sinus bradycardia may be due to intoxication, asphyxia, anoxemia, drug action or increased vagus tone. It is often seen in convalescence from the acute infectious diseases. The blood pressure changes may be rather slight. At times, however, rather sharp drops in both systolic and diastolic pressures occur. The drop in diastolic pressure is apt to be especially marked. Such sharp drops are apt to be associated with marked cerebral anemia. In consequence, dizziness, syncope or convulsive seizures may supervene. Wolferth calls attention to Gallavardin's studies. The latter has found that in certain bradycardias the diastolic pressure drop is out of proportion to the drop in systolic pressure. He calls this type diastolic pseudo hypotension. He thinks that it is due to the continued outflow of blood from the arteries during the long diastole. He has therefore suggested that diastolic hypotension be differentiated from true hypotension by the abruptness of the descent from the maximal to the minimal diastolic level, rather than the actual minimal pressure obtained.

*Heart block* The blood pressure findings in heart block vary not only according to the underlying cause, but also according to the degree of block present. Thus in transient incomplete block there may be very marked hypertension. In complete block the diastolic pressure is apt to be very low. In cases of complete block, associated with the Stokes-Adams syndrome, the blood pressure is apt to be very low, particularly during the syncopal attack.

*Premature contractions* The extrasystoles as a rule are less forcible than the normal cardiac contractions. The ventricles are less well filled. Hence their systolic pressure level is lower than that of the regular contraction. Both experimentally and clinically it has been shown that premature contractions are frequently induced by increased arterial tension and reduced in number when tension is diminished. Norris says that the existence of hypotension in association with premature contractions, other things being equal, is evidence of the functional nature of the arrhythmia.

*Auricular fibrillation* It is of course impossible to estimate systolic and diastolic pressures accurately, with available clinical means, during periods of auricular fibrillation. The pressure varies from beat to beat. Some beats fail to reach the sphygmomanometer at all, indicating the existence of the so-called pulse deficit. Where pulse deficit exists, numbers of ventricular systoles, particularly those occurring during very rapid heart action, either fail to open the semilunar valves or else expel quantities of blood that are too small to cause palpebral arterial waves. Clinically therefore the amount of pulse deficit is regarded as an index of the degree of fibrillation. Estimations of systolic pressure during fibrillation may be made by the "average systolic pressure" readings obtained by the method of James and Hart. The pressure is raised in the sphygmomanometer cuff until all pulsations are obliterated. Pressure is then lowered 10 mm. at a time. At each period the number of beats passing peripheral to the cuff is counted. The average systolic pressure is then obtained by multiplying each different pressure tested by the number of beats passing per minute. These products are added and the sum divided by the number of apex beats per minute. The quotient gives the average systolic pressure.

Studying average pressures in fibrillation by this method Hart

(267) found that two groups of diseased hearts, the rheumatic and the arteriosclerotic, showed very different pictures

In the rheumatic-mitral stenosis group, average systolic pressures under 70 mm Hg are not at all infrequent during fibrillation. These are usually cases with rapid heart rates (over 140), and a marked degree of cardiac insufficiency. With improvement, the blood pressure rises and may reach 120 mm, rarely 140. In the arteriosclerotic group, with fair compensation, the average systolic pressure is usually 160 mm or over, and only falls below this when insufficiency becomes evident. In this group, during fibrillation, if the average systolic pressure falls below 140 mm, myocardial failure is very threatening.

From the point of view of prognosis in fibrillation, Hart thinks that, so far as blood pressure findings are concerned, one may say that average systolic pressure of over 110 mm in the rheumatic group, and of over 160 in the arteriosclerotic group, are of good omen. A falling average systolic pressure makes the outlook graver.

*Alternation* It is now generally agreed that persistent alternation of the pulse betokens a myocardial degeneration of much gravity. Post-extrasystolic alternation and transitory alternation are not necessarily of such grave prognostic import. Alternation is apt to be found with the myocardial changes as seen in arteriosclerotic hearts and so there is apt to be hypertension in most cases showing alternation. Those cases of persistent alternation associated with hypotension have the gravest outlook. Navarro (268) regards the prognosis as extremely grave when hypotension accompanies *pulsus alternans*. This combination was seen in three of eight cases of *alternans*. All three were dead within the year.

*Valvular heart lesions* *Mitral lesions* In compensated mitral insufficiency, arterial pressure is practically normal. Norris refers to the fact, first discovered by Sahli, that the reestablishment of functional efficiency after an attack of broken compensation is not infrequently accompanied by a drop in arterial pressure. In mitral lesions this applies to both systolic and diastolic pressures. The fall of systolic pressure is much less marked after the reestablishment of compensation in aortic lesions.

Norris also points out that in compensated mitral stenosis, arterial

pressure is apt to be above the normal, owing to peripheral vasoconstriction. The pulse pressure is usually small. He suggests therefore that hypotension may be of some value in distinguishing between hemoptysis due to pulmonary tuberculosis, and that due to mitral stenosis. It is of course recognized that with the advent of auricular fibrillation in the course of mitral stenosis, the pressure picture of fibrillation supervenes so long as the abnormal rhythm lasts.

*Aortic insufficiency* The hemodynamics of aortic insufficiency have been studied intensively, both by experimental physiologists and by clinicians. The well established fact of high systolic pressure and very low diastolic pressure, with a very large pulse pressure, is of course generally recognized. Its definite explanation however is not, even now, absolutely settled. Early experimental evidence went to show that a considerable quantity of blood regurgitates into the ventricle during diastole, causing an augmented amount to be thrown out during the next systole. As the results of his studies Wiggers (269) believes that the chief drop of pressure responsible for the low diastolic pressure occurs in diastole. The collapsing pulse is brought about not by the volume of blood which regurgitates, but by the regurgitation of pressure during diastole. The pressure falls more rapidly within the aorta during diastole, and to a lower level, thereby diminishing the diastolic pressure. In the ventricles the initial pressure rises to a higher level. The rapid diastolic decrease of pressure within the central arteries causes a back flow of blood from the more peripheral arteries. This reflux of peripheral blood is largely accommodated in the large arteries and is no index of actual regurgitation into the left ventricle. Wiggers says that while it is doubtless true that some blood does regurgitate into the ventricle (the amount depending upon ventricular tonus), recent experimental evidence contradicts the view so prevalently held by clinicians that a large portion of the systolic discharge flows back in each diastole. Clinically, as is well known, the association of high systolic pressure (180–200 mm) with low diastolic pressure (60–30 mm) is strong presumptive evidence of the existence of aortic insufficiency. Norris points out that one should not speak of hypertension in aortic insufficiency unless the systolic pressure exceeds 200 mm. He also emphasizes the well known fact that in estimating the diastolic pressure

by the auscultatory method the fourth phase must be chosen as the criterion, as the fifth phase often persists to O Vaquez (270) says that the systolic pressure is not always above normal in aortic insufficiency. Indeed he thinks that the systolic pressure level may be of value in differentiating etiologic factors of aortic insufficiency. Thus, in regurgitation due to rheumatic endocarditis, the systolic pressure may not exceed 150 to 160 mm. If the regurgitation be of arterial (arteriosclerotic) origin, the systolic pressure often reaches 230 to 250 mm. This is the type of lesion where, as originally pointed out by Traube, the hypotension precedes the insufficiency. Aortic insufficiency with normal systolic pressure coming on at about the age of forty, without definitely assignable cause, should suggest the probability of a syphilitic origin of the condition.

*Difference in the systolic pressure in the arm and leg* in cases of aortic insufficiency, in the recumbent posture, was first described by Hill, Flack and Holtzman (271) in 1909. Under normal conditions, the systolic pressures in the arm and leg of an individual lying quietly in the horizontal position are equal. When the erect or inverted position is assumed the pressures in the arm and leg "differ by the hydrostatic pressure of the column of blood which separates the points of the measurements. In these postures the pressure in the arteries of the leg varies greatly, while in the arm the pressure is kept about the same by the mechanism which compensates for the influence of gravity." In aortic insufficiency the difference between arm and leg pressures in the recumbent posture has been found to be very great, and is of diagnostic importance. Rolleston (272) has reported a case with a difference of 200 mm, leg pressure 350 mm, arm pressure 150 mm.

CASE NUMBER	TYPE	CONDITION	ARM PRESSURE	LEG PRESSURE
			mm	mm
1	Lutic	Fair	140/60	300/80
2	Lutic	Fair	140/30	320/80
3	Lutic	Fair	150/40	240/60
4	Lutic	Poor	200/50	300/60
5	Rheumatic	Good	110/50	180/70

As illustrations, the above figures are given from five cases of aortic insufficiency under observation on the medical wards on the

Cincinnati General Hospital Four of these cases were of syphilitic origin, one was of rheumatic origin. Determinations were made by the auscultatory method, using the fourth phase for the diastolic reading

MacWilliam (1) calls attention to the fact that similar phenomena have been observed in conditions other than in aortic insufficiency, notably after violent muscular exertion in healthy persons, in some cases of arteriosclerosis and in exophthalmic goitre He points out that the mechanism involved is difficult to explain As the diastolic pressure is virtually if not absolutely similar in arm and leg it is evident that the systolic difference is a phenomenon of wave motion Hill has suggested a different conductance in the leg arteries, transmitting the large systolic wave more effectively than in the arm

MacWilliam thinks that there are two factors involved, cardiac and vascular That a cardiac factor plays a part is suggested by the clinical evidence to the effect that in man the difference in pressure is slight or absent in recent aortic lesions It is found chiefly in cases of compensated aortic lesion, with enlarged heart, large and powerful systolic wave and very large pulse pressure These are the conditions which are present to some degree in other instances where the arm-leg difference has been recorded Recently Bazett (273) has published the results of his experimental and clinical studies He concludes that the differential pressure is due, essentially, to the transference of kinetic energy in a fluid in rapid motion into stress, when the flow meets resistance The relative degrees of slowing induced in different vessels and the relative masses of blood concerned are both important The factor of change in the arterial walls, would explain the equalization of pressure during fever and by the use of warm baths, with attendant relaxed arterial tone

*Aneurysm of the aorta* The blood pressure in many cases of aortic aneurysm does not vary greatly from the normal Williamson (274) found that the pressure is higher in cases of simple aortic dilatation than in cases which a distinct aneurysm is present Stewart (275) has reported three cases of aortic aneurysm with low systolic pressure, very low diastolic pressure, with consequent large pulse pressure, (e g, systolic blood pressure 104, diastolic blood pressure, 26, pulse pressure 78) The blood pressure picture was not accounted for by

aortic insufficiency which was not present in any of the cases. Stewart thinks that the widening and weakening of the wall of the arch of the aorta produced a large reservoir into which the blood is forced in diastole, thus producing the very low diastolic pressure.

*The second factor, The condition of the vessel walls*

The physical state of the conducting vascular system, probably plays comparatively little rôle in the production of hypotension. As Greaves (30) points out, such rôle is limited to the effect which may be produced by flaccid and toneless muscle fibres in blood vessel walls, subsequent to the toxic influence of acute infection. It is thus a factor in certain acute hypotensions. Certain it is that a marked degree of arteriosclerosis may be present, and the individual have normal or subnormal blood pressure. Norris says that about one-third of all cases of well marked peripheral arteriosclerosis have normal pressure or hypotension. Fifteen years ago Muenzer (283) in discussing types of hypotension, called attention to the fact that low blood pressure occurred in a considerable proportion of cases of arteriosclerosis. His explanation was that in arteriosclerosis the blood flows through the vessels as does fluid through unyielding tubes. In such cases there is no periodic distention or contraction of the vessel lumen, and tension is therefore lowered. Evidence has accumulated to show that hypertension in arteriosclerosis is due to sclerosis of the systemic vessels. Sclerosis of the larger vessels is more commonly associated with lower pressures. Thus McCrae (276) finds that chronic aortitis, especially the luetic type, is usually associated with hypotension. It has also been suggested by various observers that, in general, blood pressures are apt to be lower in cases of arteriosclerosis due to toxic agencies, e.g., lead, infections acute and chronic, than in cases of the involutionary or hyperpietic types.

Of very much greater importance, so far as maintenance of blood pressure is concerned, is the

*The third factor The condition of peripheral resistance, determined by vasomotor tone*

Vasomotor stability, control and compensation are among the most important fundamental attributes of the animal organism. Such



intervascular relations must be adjusted and balanced to an extreme degree of nicety, if the bodily functions are to be normally and adequately maintained

Greaves thinks that the peripheral resistance to the blood stream is probably the most important single factor in the regulation of blood pressure. Peripheral resistance and peripheral constriction are effected through the agency of the vasomotor system, subject to the ebb and flow of vasomotor impulses. The endocrine system works in conjunction with the vasomotor system, exerting either a pressor or depressor action on vasomotor function. There is abundant clinical evidence to substantiate this view. One has only to think of certain chronic hypotensive conditions, e.g. Addison's disease, which is accompanied, and probably caused by, pathologic changes in the adrenals. Apart from pathologic changes, it is probably true that endocrine dysfunction may produce persistent hypotension, through the production of changed conditions of vasomotor tone.

Up to within comparatively recent times, it had been supposed that peripheral resistance referred to conditions in the arterioles chiefly. Recent researches however have shown that the capillaries play a very important part in the production and maintenance of vasomotor tone. It is thus apparent that discussion of hypotensive states dependent upon changed peripheral resistance and vasomotor tone is of necessity complex. There are still many gaps in the chain of evidence, but it is certainly true that our knowledge is steadily increasing as the result of accumulated experimental study and of carefully controlled clinical research. Changed conditions of vascular tone bring about with them, in many instances, changed conditions of blood pressure. Such changes may be in the nature of elevation or depression of the blood pressure curves. For obvious reasons, discussion here is limited to conditions of hypotension.

*Syncope* In cardiac syncope the cerebral anemia results from an insufficient expulsion of blood from the heart. Such attacks are accompanied by very marked hypotension. As example, reference may be had to the syncopal attacks forming part and parcel of the Stokes-Adams syndrome, as seen in association with heart block. But syncope may be due to vascular changes, and cerebral anemia and hypotension often occur without cardiac lesion. Marked relaxa-

tion of the arterioles may diminish the amount of blood in the larger arteries, or a loss of tone in veins and capillaries may reduce the amount of blood sent to the heart. Sudden changes in the tone of the abdominal vessels are particularly apt to induce sudden hypotension—with its resultant symptoms. The “sinking” faint feeling that follows sudden emotional shock is an instance in point. The syncope that sometimes occurs when a patient stands after an ascitic accumulation has been tapped, is another.

There is usually marked cerebral anemia during a period of *vomiting*. Brooks and Luckhardt (374) note that vomiting is accompanied by marked changes in circulation and by interference with respiration. They found that while there is occasionally a period of increased systolic pressure before the actual vomiting, there is as a rule a sudden and very marked drop, with cardiac inhibition at the moment of emesis. Great variations of the blood pressure as found during vomiting are probably due to the cerebral anemia.

*Abnormal vasomotor tone* Eppinger and Hess have focussed attention on the functions of the vegetative nervous system by their hypothesis that in certain individuals, the balance between the parasympathetic and the sympathetic portions of the autonomic nervous system is upset. If the parasympathetic (extended vagal system) is in a state of hyperactivity, its tonic action on the tissues it supplies is exaggerated. Conversely, overactivity of the sympathetic system produces increase in tone and irritability in the sympathetic realm. To these conditions they have given the names of vagotonia and sympatheticonia, respectively. Any extended discussion of the voluminous literature which has appeared regarding this hypothesis would take the present writing too far afield. It may be remarked however that these writers assume the antagonism between the two parts of the vegetative nervous system to rest upon pharmacological rather than anatomic grounds. The entire vegetative nervous system is under the control of the glands of internal secretion. Thus the chromaffin system is closely allied to the sympathetic system. Epinephrin, which produces effects similar to those resulting from experimental stimulation of the sympathetic, has no direct action on the parasympathetic system. Speaking generally, individuals in the vagotonic group have low blood pressures, while cases of sympatheticonia have high blood pressures.

The consensus of opinion in the recent literature, based upon careful clinical and experimental study, is that Eppinger and Hess have *not* proved their case. Vincent (375) sums up the generally accepted viewpoint of today when he says that "the theory as a whole is highly speculative, is based on a false analogy, and has little or no experimental or clinical evidence in its favor."

*Vascular crises* Viewed in the light of disturbed vasomotor control, the so-called vascular crises as studied by Pal and others, become more readily understandable. A vascular crisis may be brought about by abnormal contraction or dilatation in a given vascular domain. Such changed arterial tone may produce a chain of symptoms either locally, or at a distance from the vascular abnormality. In other cases general vascular phenomena may arise. From the clinical point of view most of the vascular crises are attended by marked rise of blood pressure. As an instance the rise in pressure during an attack of angina pectoris may be cited. It is recognized that between the attacks of angina the pressure may be normal or very slightly raised. While there is still discussion as to the pathogenesis of angina pectoris, there is little doubt that the attack itself is largely the result of impaired vasomotor control. In a recent discussion of the mechanism of angina pectoris Reid (277) points out that attacks are usually initiated by exercise, physical or mental. Ordinarily during exercise there is a dilatation of the peripheral vessels, produced, in large part at least, by the cooperation of the nervous system, probably by a reflex through depressor fibres in the vagus. In this way there is, normally, a drainage of blood away from the heart, so that the organ is able to contract without unusual strain. According to Reid the sequence of events in angina may be the failure of this reflex dilatation of the peripheral vascular bed, resulting in sudden rise of pressure in the first part of the aorta and the left ventricular cavity. The heightened pressure irritates the nervous connection, hence the pain. According to this view the essential feature of angina is a failure of the protective mechanism of reflex dilatation of the peripheral blood vessels when the stress arises.

Other instances of vascular crises are intermittent claudication, erythromelalgia and Raynaud's disease. Adson and Brown (278) report a case of Raynaud's disease successfully treated by bilateral

ramisection and ganglionectomy, in conjunction with bilateral perivascular sympathetic neurectomy of the common iliacs. Following operation there was evidence of vasodilatation, increased arterial flow and relief from subjective and objective manifestations of the disease. Quantitative measurements of skin temperature and calorimetric studies of the heat radiation of the feet indicated definitely maintained vasodilatation. Leriche and Fontaine (279) observed a change in arterial pressure in fifteen cases after ramisection. The operation consisted in severing the rami communicantes of the stellate ganglion and intermediate ganglion (when present). A transient increase of arterial tension appeared only on the operated side and was soon followed by hypotension. This was explained by assuming the existence of centripetal nerves in the vascular adventitia, real pressor nerves controlling the arterial tension. Stimulation of them causes hypertension, severing them induces hypotension. The occurrence of vasomotor reflexes on both sides is probably due to the existence of only one vasomotor center in the medulla. The return of the arterial tension to normal within a certain time after the operation may be ascribed to the fact that the vascular tonus is thereafter regulated only by the centripetal fibres of the intact side. Discussing high blood pressure, Pal (280) says that it is caused by functional change in the arteries (predisposition to excessive contraction). It starts with vascular crises which may be overlooked by the patient. Later on the pressure remains permanently high. He uses the term hypertension to designate high pressure in the arteries and the term hypertonia for the increased tonus of the arterial wall, which may persist even if the blood pressure is low, as in conditions of cardiac failure. The primary permanent hypertonia is an *angiotonic neurosis*, which causes severe anatomic lesions. Its frequency has increased of late, which, according to Pal, is evidence of its psychogenic origin. With reference to hypotension Pal (281) says that there can be hypotension with hyper- or hypovascular tone. In the first instance the hypotension is cardiac in origin, in the second it is due to the changed vascular tone itself. Such changed vascular tone may lead to abnormal distribution of the blood mass. Thus, if there be defective splanchnic innervation, there may be abdominal stasis with its resultant symptoms. It must be admitted however that a definite

explanation of the mechanism by which the peripheral resistance becomes defective in cases of persistent hypotension, is not perfectly understood. It is not known how far such conditions are mediated through the nervous system, how far due to the direct influence of chemical agents. As has been suggested in the section on essential hypotension, the theory of continued histamin poisoning by its action on arterioles and capillaries has much to recommend it. But even granting that it be an important factor there is no proof available that it is the only factor involved in the production of diminished peripheral resistance. Faber (282) feels that the endocrine system in its proper functioning, is the agency that controls blood pressure. Discussing high blood pressure, he says that recent researches have gone far to substantiate the conception of arteriocapillary spasm, hypertension, arteriosclerosis and visceral sclerosis, as the sequence to explain abnormally high blood pressure. His own research has convinced him that all the endocrine glands are so closely connected, that disease in one induces symptoms in some of the others. Disease or physiopathologic change in the hormone-producing organs induces a rise in blood pressure as a chemical reaction. Testimony is accumulating to suggest that the point where this reaction is started is in or near the pituitary. If the functioning of the majority of the endocrine glands is reduced, *the blood pressure is generally extremely low*.

*The capillaries and blood pressure* Within recent years much attention has been paid to the capillaries and their rôle as an important part of the cardiovascular mechanism with reference to tissue nutrition. An excellent summary of the evidence at hand concerning functional activity of capillaries and venules is given by Hooker (284). He points out that the simple hypothesis of vascular control by means of functional activity on the part of the arterioles is inadequate to explain all of the reactions involved. It is to be borne in mind that the evidence concerning capillary function is not all in, as yet. So far, demonstration of independence of function by capillary and vein has been had. No adequate attempt to correlate all available data with clinical conditions has been made as yet. Epochal work concerning the anatomy and physiology of the capillaries has been done by Krogh (259) and his colleagues. Data concerning capillary function, as here given, are taken from Hooker's review and Krogh's book on the anatomy and physiology of the capillaries.

Indisputable evidence has been brought forward by Krogh and others to show that the capillaries possess powers of dilatation and constriction independently of the arterioles. It has also been shown that the calibre of the capillaries is much smaller when the tissue supplied is at rest, than when the tissue is active. This would indicate that the capillaries exist in a condition of constrictor tone. Thus it has been shown that in resting muscle comparatively few capillaries are visible. They are evenly distributed and form an elongated mesh work along the fibers. When the muscles contract either spontaneously or as the result of stimulation many more capillaries spring into view, to disappear when the muscle comes to rest again. Krogh has shown that during activity, the total capacity of the capillaries of the muscle may be increased from 0.02 per cent to 15 per cent of the total volume of the muscle. It has also been shown that blood corpuscles often force themselves through capillaries having diameters much smaller than the corpuscles. In order that they may pass, the corpuscles become folded and the capillaries deformed in shape. The great variation in the number of patent capillaries according to activity of the tissues shows that the oxygen supply must become altered to meet the varying demands. Krogh has shown by careful measurements that the oxygen pressure necessary to supply the muscle fibres is very small, even during periods of great activity. The call for oxygen by the tissues is readily met by diffusion from the capillary blood.

With reference to the mechanism of varying constriction and dilatation of capillaries, it may be said that the two factors entering into consideration are nervous and chemical stimulation. In general terms, up to this time it has been believed that nervous stimuli cause only constriction. Chemical stimuli may mediate both constriction and dilatation. The effects produced on the capillaries as the result of stimulation of various kinds are in some instances the results of the interplay of several factors. Thus heat and cold produce respectively relaxation and constriction of the capillaries, as of the arterioles and venules, acting in part through the nerve supply to them. On the other hand ultraviolet light acts directly on the capillaries, causing a slowly appearing and long continued dilatation, inducing the well known erythema. Many chemical substances introduced into the

blood stream have direct and marked action on the capillaries. As long ago as 1907 Heubner (285) had shown that the intravenous injection of the double chloride of gold and sodium produces a shock-like prostration accompanied by marked engorgement and stasis of the capillaries and veins. Dale and his colleagues (286) (287) (288) came to the conclusion that histamin is a capillary poison producing an effect upon the general circulation through the capillaries, analogous to that induced by the injection of gold salts. Cannon (51) has stressed the fact that in shock the capillaries are packed with red cells. He offers this conception of "exemia" as the explanation of the reduction in blood volume, the "lost blood" that is such an important factor in shock. The amount of blood which under circumstances can be "stored" in the capillary bed instead of being returned to the general circulation has been shown to be extremely large. Hooker (284) has shown that histamin dilates the venules as well as the capillaries. Experimentally, he showed that in histamin poisoning there is a fall of venous pressure corresponding in magnitude to the drop in arterial pressure. He concludes that dilatation of capillaries and venules must be able to accommodate a very large amount of blood, since the pressure in both artery and vein falls too quickly to be wholly accounted for by transudation of plasma into the tissue spaces.

Krogh has brought forward very suggestive evidence that the capillaries are normally kept tonically contracted by a substance present in the blood stream and he feels that there is good reason to believe that this substance is the pituitary hormone. In a beautifully conducted series of experiments Krogh and his associates (289) showed that there is present in the blood of mammals a substance which is capable of maintaining the tonicity of the capillaries in the interdigital membrane of the frog. Perfusion experiments verified the findings. Extirpation of the entire hypophysis caused marked dilatation of the web capillaries, which persisted for weeks. When only the anterior lobe is removed this dilatation does not follow. Krogh believes that the pituitary hormone is the substance in blood which maintains capillary tone. If a similar control of human capillaries can be shown, the therapeutic value of pituitrin in conditions of shock would be apparent. Apparently epinephrin does not have a comparable action.

Concerning the actual pressure in the capillaries, there is still no agreement among investigators. "Capillary pressure" according to different observers is represented as anywhere from 25 to 50 mm H<sub>2</sub>O and 70 mm Hg. At least four methods of estimating capillary pressure have been tried (MacWilliam) (1), (1) Blanching of skin of finger or hand, (2) pressure required to cause obliteration of capillaries under the microscope, (3) Pressure required to cause stasis of corpuscular flow under the microscope, and lastly the method of Carrier and Rehberg, carried out in Krogh's laboratory. In this method a capillary loop is pierced with a very fine glass needle containing saline at a measured pressure. The figures obtained by this method, unfortunately not suited for clinical study, are relatively low and lend support to Hill's contention, repeatedly made, that normally the capillary pressure is low. MacWilliam (1) rightly emphasizes the fact that even supposing that capillary pressure can be accurately measured, there still remains the question of the application of such results to the conditions of the general circulation. There are as yet no means of ascertaining the relations between pressure measurements in the skin and the pressures existing in the capillaries of the internal organs. It is pointed out that it is obviously not permissible to speak of capillary pressure in the same sense as arterial pressure. Arterial pressure is a definite measurement virtually the same in all the large arteries throughout the body, while capillary pressures vary very widely in different regions under physiological conditions.

The clinical applications of recent studies of the capillaries are naturally far reaching. As has been intimated, there has not been a complete correlation of experimental studies and clinical observation. Hooker (284) concludes his article with the following suggestive summary:

We have seen that the capillary bed is responsive to both chemical and nervous influences. Broadly speaking we may say that chemical factors, so far as they have been studied, mediate dilatation of the capillaries and venules, while nerve stimulation mediates constriction of these vessels. Both these factors have long been recognized as participating in vascular reactions, but only in recent times have they come to be specifically located in their effects upon the capillary and venule, that is, upon that section of



the vascular bed which is composed of bare endothelium. We may believe that the chemical regulation is usually local in character, producing changes in accordance with the passing needs of particular tissues, and that only in special or pathological conditions does the reaction extend to the body as a whole. In accordance with this view we might regard the nervous control as a force tending to restrict the capillary beds over the body as a whole, thus maintaining a tone to be played upon by chemical factors. But the story is far from complete and much remains to be done. This much, however, appears true, that we must reorganize our conception of the peripheral resistance. Hitherto the functional peripheral resistance has been limited to the arteriole, the caliber of which is controlled by a muscular coat subject to nervous and chemical influences. The resistance to the flow of blood by the capillary and venule has been regarded as essentially fixed. Now we know that beyond the arteriole, the capillary and venule function actively and must therefore participate directly in vascular reactions. Whether it will be shown that these several areas of the peripheral vascular bed function independently of one another is an interesting question for the future.

Some of the recent clinical studies of the effects of the capillaries as an important factor of the cardiovascular mechanism may be here cited.

Reference has already been made to the rôle of the capillaries in the production of wound and surgical shock. (See section on wound shock.) The fundamental importance of the capillaries in the production of shock have been particularly emphasized by Cannon and Dale. In his discussion of traumatic shock Cannon (51) has shown that among the sustaining factors of shock, after low pressure has developed, in consequence of the action of initiating factors, dilatation of the capillaries helps to continue the state of shock, and therefore the hypotension. He has also demonstrated the probability of a series of vicious circles, all having to do with the capillary circulation, and all tending to keep up the condition of shock and hypotension. (Quoted in detail, section on Surgical shock.)

Based on Dale's studies of histamin-capillary poisoning, the present writer has postulated a theory to explain the low blood pressure in cases of so called essential hypotension (See that section.) Boas (290) emphasizes the fact that it is in the capillaries that the exchange

of substances necessary to the life of the body cells and the waste products of metabolism, takes place. It is because of an abnormal flow of blood through the capillaries in various parts of the body that symptoms of disease arise when the circulation is impaired in whole or in part. Heart failure sufficient to cause chronic passive congestion of the viscera is of significance because the stasis of the blood in the capillaries interferes with the metabolic activities of the organ involved and results in symptoms referable to malfunction of that particular viscus. The blood flow in the capillaries is therefore a measure of the efficiency of the circulation.

Olivecrona (291) has shown that experimental peritonitis in rabbits, cats and dogs leads to typical circulatory shock, showing the rapid pulse, low blood pressure, cyanotic pallor and the characteristic reduction in the volume of circulating blood. Evidence is presented to show that this form of shock is due to poisons, probably disintegration products of proteins, liberated into the blood (capillary poisons).

Douglas (292) has made studies on the nature of the shock occurring after burns. He refers to the work of Cevario (293) who joined rats in pairs by lateral coeliotomy. One of each pair underwent experimental scalding of a part of the skin. Both animals suffered to the same extent, showing that toxic substances circulating in the blood must be responsible for the symptoms. The marked drop in blood pressure, the rapid and weak pulse and the diminution in blood volume are well known clinical features of severe burns. Douglas' studies have convinced him that the constitutional shock symptoms of burns, occurring before the period of infection, are due to material absorbed from the surface. He calls attention to the enormous capillary bed (under normal conditions potentially closed) that is opened up quickly, by a first or second degree burn. From the standpoint of therapy, Douglas calls attention to the fact that prompt and lasting restriction of the rate of flow and of exchange in capillaries may be produced over large surfaces devoid of epithelium by constant or intermittent local application of vasoconstricting drugs. The capillary and arterio-venular beds may be reached through unbroken skin by appropriate local diffusion methods without subcutaneous injections. The vessels underlying a superficial burn of the human skin respond readily

to pressor drugs after such procedures, the pressor action being distinctly stronger than the dilator forces at work

Experimental and clinical results indicate that epinephrin locally applied will largely, if not completely, prevent its own absorption through direct action on the first vessels not severely injured. Restriction of the rate of exchange and flow in the capillaries by such means prevents the local absorption of harmful agents into the general circulation until such time as they may be dealt with at the site of their formation. In extensive burns such treatment should prevent the severe shock, with all of its attendant dangers. In a later communication Douglas (294) describes his method for testing the action of pressor drugs on superficial vessels. He found that epinephrin, locally administered in proper concentration, on the denuded ear of a rabbit or guinea pig, produces a peripheral vascular block so complete, as to prevent absorption of a toxic dose of strychnin sulphate in saturated solution. In similarly prepared control animals enough strychnin was absorbed in identical periods of time to produce convulsions in every animal and death in a majority. The effect of mechanical stimulation is thus ruled out. After intermittent applications of epinephrin for two hours and ten minutes it is still active in preventing the absorption of strychnin. The vasoconstriction is therefore not relaxed in the period of time during which an effective concentration of epinephrin is present. Swelling of tissues and decreased permeability from mechanical causes cannot account for these results, as each control animal developed symptoms when physiologic sodium chloride was substituted for epinephrin.

Manfredi (295) studied the effects of subcutaneous injections of epinephrin on the capillary circulation in man. He observed at first a spasm, then a relaxation of the capillaries. In the latter stage, however, the vessels were rather less visible than before. Redisch (296) found a more intensive contraction of the capillaries, in two cases of diabetes, than in healthy persons. The contraction lasted twice as long as usual. Injections of ovarian extract caused, in these cases, a dilatation of the capillaries and a lowering of the blood pressure. The two hormones showed a certain antagonistic action.

Klotz (297) says that the circulating system is dependent on two

motive forces one is the heart, the other is the capillary network, especially that of the splanchnic region. Circulatory depression may result from disturbance of either force. In cardiac depression, cardiac tonics are indicated. But when the capillary network is involved the best remedy is pituitary extract. This substance is a capillary constrictor. It is thus of value in "congenital asthenia with hypotension," and in hemorrhage. Its value in the intestinal paralysis of peritonitis depends upon its capillary constricting action. Brown (298) studied the skin capillaries in a series of fifty cases of severe cardiovascular renal disease. The most constant changes noted were contraction or narrowing of the arterial and venous limbs producing a small contracted type of capillary, frequent invisibility of the arterial limb producing a hooked shaped capillary loop, and thirdly marked disturbance of the capillary flow, with frequent disappearance of single or multiple loops. Hisinger-Jaegerskjoeld (299) in an examination of 17 patients with valvular defects, 11 with myocardial disease and 6 with aortitis or aneurism of the aorta, found normal capillaries in the cases in a state of maintained compensation. He believes that the capillary circulation affords a reliable index of the condition of the general circulation. Hesz (300) made comparative examinations of the blood in arteries, veins and capillaries. He found that normally the venous and capillary bloods contained the same quantity of erythrocytes, while arterial blood often contained a greater number. Heart lesions seem to increase the number of red cells in the capillaries. Artificial venous stasis is followed by an increase of red cells in veins and capillaries and a decrease in the arteries. He endeavored to find out whether the rise of blood pressure after injection of epinephrin causes a change in blood concentration. The number of red cells in arteries and veins is increased. In the capillaries, however, it is diminished. He concluded that changes in concentration are not due to the changes in blood pressure. In the light of recent researches this conclusion seems justified, only it does not go far enough. The real conclusion, which these studies would indicate, is that changes in blood pressure are due to changes in blood concentration. *With dilatation of the capillaries the blood pressure falls, with capillo-constriction it rises.*

## HYPOTENSION IN RELATION TO ENDOCRINE DISTURBANCES

*The adrenals*

Despite a very considerable amount of careful experimental study, many phases of the physiology of the adrenals are still unsettled. So competent a physiologist as Carlson (306) has summarized the situation by stating that "the question of reflex and central control of the suprarenal nervous mechanism is unsettled. Competent investigators have reported absolutely contradictory results, and clinical opinions bearing on the question are mere guessing." So far as the present discussion is concerned, the relation of the adrenals to the circulation is of particular importance. Here, as elsewhere, in the discussion of adrenal function and mechanism, there is no unanimity of opinion. Certain points of view are now accepted in principle, though even the advocates of these views freely admit that the final word has not been said as yet as to details. It is interesting to find, as one reads the literature, the cautious reserve of the strictly physiologic point of view as contrasted with the always sanguine and frequently unwarrantably definite views of the clinicians. This difference in viewpoint moves Stewart (307) to exclaim with some bitterness that

A rank growth of "endocrinological" speculations sprang up during the war, which developed so many novel medical problems, all of course pressing for solution, few of which could be quickly solved. But hypotheses could be quickly framed, especially when the framers were not hampered by any excess of critical faculty or exact physiological knowledge. The most recent "ology," endocrinology, was naturally pressed into the service. Much of this speculation found its way into print, in spite of the scarcity of paper, and scarce paper was sometimes ill applied in this service.

Hoskins (308) contributes a careful résumé of existing views as to the relation of the adrenals to the circulation. His conclusions are here quoted in full.

The adrenal glands have a definite pharmacologic relation to the circulation by virtue of their production of adrenin. Adrenin causes stimulation of the heart, vasoconstriction in the splanchnic and cutaneous regions and dilatation in the skeletal muscle. Increased or decreased blood pressure

may result, depending upon dosage and various accessory factors Adrenal extirpation with its resulting circulatory collapse proves the existence of a physiologic relationship also This collapse is not entirely, if at all, due to adrenin lack, since it cannot be long forestalled by administration of the drug and it does not ensue when adrenin secretion is reduced below detectable limits The slow development of the symptoms of epinephrectomy also indicates that they are not due to sudden failure of adrenin as a stimulating substance Direct experimentation shows that adrenin often depresses sympathetic irritability Marked symptomatology develops while the sympathetic system responds well to stimulation If adrenin deficiency is a factor, it probably operates in the effector rather than the conductor mechanisms The adrenals are stimulated to secretion by splanchnic nerve irritation, hence are supposedly under central control Evidence of the existence of an adrenal center immediately caudad to the corpora quadrigemina has been reported The preponderance of the evidence indicates that adrenal depression is evoked by stimulation of the vagus or depressor nerves and augmentation by asphyxia, pain and emotional excitement This augmentation results in a mass shifting of the blood from the skin and viscera to the organs involved in neuro-muscular exertion The cortex is probably the indispensable part of the adrenal The medulla apparently serves merely to reinforce the sympathetic system in times of stress

It seems to be fairly generally agreed that the tonus hypothesis, viz that arterial tone is maintained by the epinephrin constantly liberated, is not supported by physiologic evidence The amount of epinephrin secreted spontaneously, would be, when diluted with the mass of blood of the entire circulation, quite inadequate to have any effect on blood pressure Also if any effect upon the vessels should occur with these minute doses, it would be one not of constriction but of dilatation in many vessels at least (McLeod) (309) Moore and Purinton (310) have shown that very small doses of epinephrin will lower blood pressure instead of raising it, a fact which had been confirmed by other investigators (314) Vincent (311) quotes Hoskins as being of the opinion that there is no reliable evidence that, under normal conditions, circulating blood contains any epinephrin at all He points out that as the technique of investigation has improved, the reported dilution of the epinephrin in the arterial blood has constantly approached infinity On the other hand, Tournade and Chabrol

(312) maintain, as the result of their experimental studies, that adrenal secretion plays an undeniable rôle in maintaining blood pressure and that the secretion is continuous through the tonic activity of the sympathetic Prusik (313) studied the effect of epinephrin on the human circulation He concludes that epinephrin in human beings sometimes strengthens the auricular contractions, and usually increases the ventricular contractions by direct action on heart muscle or on nerve endings themselves. By this influence on the sympathetic nerve endings the pulse rate is increased In the blood vessels of the extremities there is active vasodilatation. Contractility is increased, this being at times the only effect of epinephrin The cutaneous capillaries are narrowed and in this way resistance is raised. The blood pressure primarily rises from increased cardiac activity. The diastolic pressure falls following the widening of the large vessels in the extremities, even during strong capillary contractions

Collip (315) contributes a résumé of work done by various authors showing that a number of factors produce modification of the epinephrin reaction (Bibliography is appended) The fact that very small doses of epinephrin cause a fall of blood pressure and not a rise, has been emphasized.

Epinephrin may cause vaso-dilatation in one area and vaso-constriction in another at the same time (Hartman and Frazer; Hoskins, Gunning and Berry)

A reversal of the depressor action of epinephrin may be accomplished by lowering the blood pressure level (Cannon and Lyman).

The pressor response of epinephrin is reversed by ergotoxin (Dale).

The reversal of the depressor action of epinephrin may be brought about by injection of tissue extract or by increasing the depth of anesthesia (Collip).

Changes in hydrogen ion concentration may affect epinephrin response (Snyder, Campbell and Andrus; Collip). The pressor response to epinephrin is decreased by anesthesia (McGuigan).

The pressor response to epinephrin is increased following hemorrhage (McGuigan)

The mode of administration affects greatly the response to epinephrin Moog and Ambrosius (316) studied the action of epinephrin on the capillaries, using the capillary microscope They found that

after the injection of epinephrin only the arterial part of the capillary shows contraction. The blood stream becomes slower, and the tissues get less blood. Studied with the skin microscope after epinephrin injection, the capillaries have a granular aspect. Contraction of the capillaries occurs only when there is a blood stream in the capillaries. When, for example, the blood stream is temporarily arrested by tying a cord around the limb, epinephrin does not produce contraction. They do not believe that epinephrin is decomposed by the tissues, because if it be injected into a limb tied by a cord the action of the epinephrin may be visibly observed ten to twenty minutes later, when the cord is removed.

Killaway and Cowell (317) studied the antagonism in action between histamin and epinephrin. They found that animals with marked adrenal insufficiency are often prostrated by a minute dose of histamin, but this does not occur if epinephrin is previously administered. They hope to be able to differentiate the part played by adrenal medulla and cortex in this phenomenon. Wislocki and Crowe (318) confirmed the findings of other investigators that the medulla of the adrenals is not necessary to life, but that an animal dies quickly if the entire cortex is extirpated. Adrenal insufficiency was produced by the combined surgical removal of a part of the adrenal glands and implantation of radium into the remainder. The radium caused an area of necrosis which gradually destroyed the medulla of the adrenals and the abdominal chromaffin body, *without producing symptoms*. It was found that to maintain life it was necessary to leave a fragment of the total cortex, about one-fifth at least. Removal of all the cortex resulted in death with a terminal fall in blood pressure and temperature.

Discussing the relative importance to life of the two parts of the adrenal, Houssay and Lewis (319) conclude that the cortex is indispensable to life. It maintains its vital functions without the cooperation of the medulla. The chromophil tissue of the adrenals is not necessary to life or to normal functions. This does not mean that chromophil tissue is not indispensable to life. In experimental work only a part of this tissue is removed, and it must be remembered that, relatively, a greater portion of medullary tissue than of cortical tissue remains in the body after adrenalectomy. If chromophil tissue has vital functions, the extracapsular portion is sufficient to



maintain them, but up to now there is no evidence that these vital functions exist

Bru (320) studied the hypotensive and hypertensive action of adrenal cortex and medulla, respectively. He injected dog adrenal medulla tissue, and cortex tissue intraperitoneally into rabbits. He then injected the serum of these rabbits intravenously into dogs. The effects appeared in four to five minutes and lasted for more than ten minutes. Injection of 10 cc of anticortex serum caused a slight lowering, injection of antimedulla serum a slight rise, in blood pressure.

Platz (321) studied the action of epinephrin in the human being. The intravenous injection of epinephrin nearly always first raised and then lowered blood pressure. When the blood pressure was first increased, 0.005 mgm would produce a marked reaction, even 0.001 mgm was enough to produce a change in blood pressure. Given subcutaneously, the minimum active dose was 0.1 mgm. When atropin or papaverin were given with epinephrin, the rise of blood pressure was much higher than after the injection of epinephrin alone. After the intravenous injection of epinephrin 94 per cent of the patients showed an increased pulse rate, 6 per cent a lowered one. No case was noted in which the pulse rate remained unaltered. Respiration became more frequent in 80 per cent of the cases and less frequent in 20 per cent. Similar changes were noted after subcutaneous injection of epinephrin. Danielopolu and Carniol (322) studied the effects of the intravenous injection of epinephrin on the normal man. Accounts of epinephrin ranging from 1:50,000 to 1:250,000 were injected into the subject in the reclining position, and records were made of the blood pressure. The authors conclude that epinephrin is not a specific sympathetic stimulant, but that it induces reaction in the entire vegetative system. Because of rapid destruction, intravenous administration is preferred to subcutaneous. The intravenous injection gives rise to three groups of phenomena. Modification of cardiac rhythm, modification of arterial tension, and subjective disturbances. All these occur when the strong dose of 1:100,000 is given. When weaker doses are administered, the cardiovascular phenomena alone appear. There is, at first, cardiac acceleration, then depression, as the dose becomes smaller.

DeAngelis (323) studied the effect of the administration of epineph-

nm in sick children. He found that injection of 1 cc of 1:1000 solution caused a rapid rise of blood pressure in sick children. This was manifest after the first ten minutes, reaching its maximum in 30 minutes, and slowly decreasing in from  $2\frac{1}{2}$  to  $3\frac{1}{2}$  hours. Children with cardiac or cardio-vascular disorders showed a reaction less marked and of shorter duration than did normal children. The pulse showed initial acceleration, followed immediately by retardation, but with the maintenance of high systolic tension.

*Radiation of adrenals.* There have been various reports of the action of the X-ray on the adrenals. One group of investigators found definite changes in blood pressure (hypotension), another group found changes in the sugar metabolism following radiation. Still another group obtained no definite results. David and Hirsch (324) studied the epinephrin content in guinea pigs, rabbits and dogs, 40 in all. In each case, one adrenal body was isolated and exposed to the rays, in dosage of a definite, measured, quantity, while the other adrenal was thoroughly protected from the rays. The application of rays varied from one skin dose to one-fourth skin dose. The authors conclude that the adrenal system is influenced by radiation with the X-ray, that a distinct lessening of function is obtained by a radiation of one skin dose, that an increased function is obtained by radiation of one fourth skin dose.

*Epinephrin and absorption.* Douglas (325), continuing his studies on the relation of epinephrin and absorption (see section on Capillaries) finds that epinephrin, in consequence of its vasomotor action, exerts a restraining or retarding action on the absorption of poisons by the capillaries. This action is observed in absorption of the following substances: strychnine sulphate, pure strychnin, pure nicotin, cocain hydrochlorate, pure strophanthin, nitrate of aconite and various staining agents. By the same mechanism, epinephrin may definitely preserve guinea-pigs, inoculated with doses of cobra venom fatal to control animals. The vasomotor action of epinephrin is also opposed to the effects of the inoculation of tetano-toxin. In the control animal, deprived of epinephrin, the inoculation of the same dose produces tetanus. The influence of epinephrin may be observed in eroded skin, the mucosae (tongue, stomach, duodenum, jejunum, ileum, appendix) the meninges, the pleura, the peritoneum and the muscles.

*Adrenal insufficiency*

Stewart (307) has made a résumé of the subject of adrenal insufficiency, discussing the problem from both physiologic and clinical viewpoints. A reading of the evidence as here presented shows very definitely the confusion of thought and the divergence of opinion which exists. He emphasizes the fact that it has not been possible to produce experimentally any well characterized symptoms associated with partial adrenal insufficiency. And he adds that, in experimental work, little real progress has been made in discovering definite quantitative or qualitative alterations in the metabolism, or in relating such alterations as have been assumed to occur, to the fatal adrenal insufficiency. He insists that the rapidly increasing weakness and the fall of blood pressure in animals hastening to die (after more or less complete adrenalectomy) are not sufficiently specific symptoms to make it very safe to link them up with the loss of adrenal function. In animals which survive with a vast anatomical deficiency in adrenal tissue, it is very difficult to unveil any signs of corresponding physiological insufficiency. It is of interest to note that Elliott (326) was unable to note any alteration in the mechanism of the heart beat during the gradual failure of the circulation in cats after total adrenalectomy until death. There was no paralysis of the skeletal muscles or their nerves, and no paralysis of the cardiac vagus fibers. But when the animals had become very weak and were moribund there was some paralysis of the efferent vasomotor nerves.

Discussing the much mooted question as to whether experimental adrenal insufficiency is due to loss of cortex, or of medulla, or of both, Stewart holds that the experimental evidence has tended more and more to show that the cortex is the part of the adrenal indispensable to life. Stewart adverts to the fact that clinicians in writing on adrenal insufficiency seem to ignore this fact. To them, adrenal insufficiency seems to connote merely interference with the output of epinephrin, and consequent derangement of function in which epinephrin is *assumed* to play a leading rôle. Stewart is emphatic in his assertion that there is *no* evidence that diminution in the ordinary rate of epinephrin output or even its total suppression can give rise

to symptoms As illustrating the point, two clinical case reports may be cited Creyx and Ragot (327) report two cases of sudden death in which autopsy showed the adrenals to be nothing but blocks of caseous material, without a trace of normal tissue There had been no premonitory symptoms, and the authors stress the point of view that sudden death may occasionally be the first sign of adrenal insufficiency Boyd (328) describes the case of a soldier who died while on leave of absence He had been performing his duty in a training camp and showed no signs of Addison's disease The autopsy showed that the lungs were tuberculous The adrenals were converted into structureless masses somewhat larger than the original glands On the right side neither cortex nor medulla could be found On the left side a narrow strip of cortex, not more than two mm in width was present at one point, but there was no medullary tissue The author attributes death to acute adrenal insufficiency In his comment, Stewart strongly objects to this He points out that the absence of any symptoms or signs of adrenal insufficiency, as in the cases reported, makes a diagnosis of adrenal death purely hypothetical He adds that the only safe conclusion to be drawn from such cases is that the medulla is not essential to life, while the preservation of only a very small portion of the cortex may be compatible with apparent health and vigor

Discussing a suggestion of Byrne (329) that hypertrophy of the adrenal, mainly of the cortex, in soldiers dead from the effects of underfeeding in a German prison camp was compensatory, in order to restore the blood pressure lowered by the want of food, Stewart insists that the authors ignores two fundamental facts First, that the epinephrin is given off from the medulla and not from the cortex Second, the maintenance of the normal blood pressure does not depend to any important degree upon epinephrin Stewart insists that arterial hypotension is not caused even when the epinephrin output is totally suppressed Fatal adrenal insufficiency is produced in animals, in all probability, by interference with the cortex

Discussing clinical types of adrenal insufficiency, Sézary (330), describes three types (a) the fulminating, rapidly fatal form, (b) the monosymptomatic form (myasthenia or amyotrophy), (c) a form including diverse sets of symptoms including the acute syndrome of

Sergent-Bernard, and the subacute or chronic form, including Addison's disease and its varieties. Tuberculosis may induce any one of these syndromic forms. Syphilis often attacks the adrenals. So, also, does the virus of typhoid, diphtheria, and other acute infections. In the treatment of these conditions, Sézary calls attention to the value of specific treatment where this is possible, e g , antitoxin for diphtheria, quinine for malaria, etc. Rest and adrenal extract are of value whatever the type of infection. The extract of the whole gland is better than epinephrin. He reserves epinephrin for acute disturbances with cardiac collapse and recommends subcutaneous administration. The dose is gaged by the therapeutic results obtained with the first doses and by the signs of intolerance. A rise in blood pressure is a good index of the efficacy of the opotherapy. The fact that the pressure does not rise at once does not prove that the drug has been ineffectual. Increase in muscular strength as tested by the dynamometer at frequent intervals, is a favorable sign. The appearance of tremor calls for caution. Glycosuria, albuminuria and circulatory disturbances, require suspension of treatment. In some cases the doses have to be high and kept up for several weeks, even for months, before good results are obtained. In such cases, signs of intolerance should be watched for with especial care. At times the addition of pituitary extract is of value, when adrenal extract alone fails. Sézary believes that as our knowledge of the subject increases, so that the diagnosis of the condition may be made earlier, surgical removal of the affected parts of the adrenals may prove to be of great value. In a later communication Sézary (331) criticizes the present tendency to see insufficiency of the adrenals in every patient who presents one or two symptoms which are also present in Addison's disease. Pigmentation of the skin, even when associated with asthenia is not sufficient for the diagnosis. He also points out that the presence of the Sergent's white line in the skin (q v) is not a sign of adrenal insufficiency. Sergent (332) says he has been publishing data on adrenal insufficiency for twenty-five years, but admits that the interpretation of the facts observed requires revision. Extreme adrenal insufficiency induces a clinical picture suggesting acute poisoning. Toxic disturbances characterize inadequate function of the adrenals. The acute toxic disturbances are of various types,

suggesting acute poisoning, meningitis, peritonitis, or cholera. Chronic insufficiency is revealed by hypotension, bronzing of the skin, and asthenia in which the muscles show exceptionally rapid and intense fatigue when measured by ergograph or dynamometer. This fatigability is the early phase of what becomes, in extreme insufficiency, painful cramps, contractures and terminal convulsions. Sargent retracts his former statements that the white dermatographia is a sign of adrenal insufficiency. He emphasizes the toxic nature of the disturbances arising from such insufficiency. Sargent and Oury (333) publish the report of a case, with autopsy findings, in which the correct diagnosis had been made clinically. The patient had suffered for seven years from chronic adrenal insufficiency. There had been marked pigmentation of the skin, asthenia and low blood pressure. The patient had never had the "white line" sign. He died in an acute attack of abdominal pain, painful muscular spasms, contractions, low blood pressure, fever, and vomiting. The adrenals were extremely atrophied and contained tubercles.

Cornil (334) believes that one symptom of adrenal insufficiency may be severe and continuous headache. The low blood pressure induces marked intracranial hypotension and the headaches result. He describes three cases of adrenal insufficiency, one due to a severe attack of influenza, one due to mushroom poisoning and one due to deep radiation of a uterine fibroma. Other signs of adrenal insufficiency were prominent, notably asthenia, severe pain in dorsal or lumbar regions, and pigmentation. In all of the cases treatment with whole adrenal extract stopped the headaches very promptly. The general health in each instance improved more slowly. Cornil found that intraspinal injection of 1 cc of adrenal extract did not raise the pressure in these cases. However a marked rise in pressure was evident within four or five minutes after intramuscular injection. Thus, he believes, confirms his assumption that arterial hypotension entails hypotension in the cerebrospinal fluid. Babonneix (335), in submitting some clinical notes on adrenal insufficiency, assigns two essential functions to the adrenals, angiotonic and antitoxic. The former maintains the blood pressure at a certain level by the output of epinephrin, a product of the medulla. The latter neutralizes toxins by the lecithin produced by the cortex. As has already been

emphasized, the view that blood pressure is maintained by epinephrin output is definitely no longer tenable, so that this portion of Babonneix's theory may be discarded. None the less his point of view has a certain interest. Adrenal insufficiency, he says, results, on the one hand in circulatory disturbances: dilatation of the ventricles, acceleration, weakening and irregularity of the heart beat, small pulse, pallor, white line and syncopal attacks. (The chief trouble with this point of view is that it is not true.) On the other hand, says Babonneix, the accumulation of undestroyed toxins produces digestive disturbances, anorexia, vomiting, colic and asthenia. This theory of the toxic nature of adrenal insufficiency is in line with the theories of other observers, notably Sergent (332). It has, at least, not been completely disproved as yet. Babonneix insists that sudden cardiac failures following acute infections like typhoid, diphtheria and scarlet fever are not due to bulbar intoxication, myocardial disease, vagal neuritis, etc., but are purely dependent on adrenal insufficiency. Cases of sudden death ascribed to aortitis or coronary artery disease are in reality due to profound changes in the adrenals, as are most cases of post-operative death or surgical shock. In the light of our recent knowledge of the facts, one cannot help feeling that Stewart expresses the situation very well. He says (307) that in reading many papers by clinical endocrinologists, especially the French and the Italians, one can "scarcely escape the feeling that here one has broken through into an uncanny fourth dimension of medicine, where the familiar canons and methods of scientific criticism are become foolishness, where fact and hypothesis are habitually confounded, and 'nothing is but what is not'."

Blumgarten (336) insists that adrenal involvement in pneumonia, typhoid and other acute infections is evidenced by tympanites, asthenia, exhaustion and low blood pressure. The asthenia, hypotension and abdominal distension indicate sympathetic paralysis and this with the Sergent's white line indicates adrenal involvement. In post-infectious adrenal insufficiency, there may be disturbance of the endocrine interrelationship. Thus, there may arise compensatory hyperthyroidism, or autonomic gastric symptoms or so-called post-infectious neurasthenia. The treatment of this form of adrenal insufficiency is, theoretically, the administration of suprarenal sub-

stance But, according to Blumgarten, this is frequently disappointing, chiefly because this substance is inert by the time the patient receives it Here again there is a lack of proof of a direct causal relationship of the adrenal insufficiency and the syndromes produced Blumgarten believes that general tonic treatment, including the use of iron and strychnin, with forced feeding, are of value He also believes that during the course of acute infection, sympathetic tonus should be increased by the injection of pituitrin and epinephrin In post-infectious adrenal insufficiency with neurasthenia, thyroid hyperactivity and vagotonic gastric symptoms, small doses of a reliable preparation of adrenal extract and the use of careful dieting and alkalies are found to be of great service On the other hand Cohoe (337) submits a brief résumé of the acute, subacute and chronic types of picture, supposedly dependent upon adrenal insufficiency He thinks that acute rapidly fatal cases are due to hemorrhage into the adrenals He refers to Addison's disease, also to the chronic functional type with asthenia, lethargy, circulatory weakness, hypotension and cold hands and feet He is conservative in his statements with reference to organotherapy with adrenal extracts He seems to agree with those who report little or no benefit from their use He distinguishes between the pharmacological effect of epinephrin as used prophylactically in anaphylactic shock, or to abort attacks of asthenia, and any supplementary rôle in so-called states of adrenal insufficiency He does not think that there is any certain evidence that adrenal extract given by mouth has any curative power Adrenal dyspepsias have been described by Loeper, Benzard and Wagner (338) and adrenopathic hyperchlorhydrias by Kaplan and Grief (339) as due to adrenal insufficiency, apparently on no other evidence than that the administration of epinephrin seems to do good As Stewart (307) remarks, it has been repeatedly emphasized by physiologists that the pharmacodynamic or therapeutic effects of epinephrin cannot be used to prove the existence of adrenal insufficiency He refers to the somewhat trenchant question of Hoskins (340) who asks whether because cascara is efficacious in relieving constipation, we ought therefore to conclude that this is because the patient is suffering from hypocalcaemia? Berman (341) refers to a group of children in whom hyperchlorhydria is produced by irritating foods Such



children, he says, are generally of dark complexion and have a tendency to low blood pressure, low blood sugar and relative abnormal fatigability. This predisposition *perhaps* depends upon a certain relation to the adrenal-sympathetic-thyroid mechanism of the organism, which controls the conductivity of nerves inhibiting or stimulating the gastric cells. Such cases do well under a hygienic regimen with removal of gastric irritants from the diet, antacids and adrenal "nucleo-protein." It might be added that in the experience of some of us the therapeutic measures as suggested, without the use of adrenal nucleoprotein, have been markedly efficacious in such cases in children.

Martinez (342) found symptoms of adrenal insufficiency in a case of gastric ulcer, namely hypotension, asthenia and pigmentation of the skin. There was also mononucleosis, absolute and relative, and vagotonia. He refers to the digestive symptoms always present in Addison's disease and says that in autopsies on such cases he has frequently found erosions of the gastric mucosa and even true gastric ulcers. He adds that Fuizi has demonstrated these lesions in dogs after extirpation of the adrenals. He explains these conditions by the increase of tonus of the vagus, which determines the increase of gastric secretion, contraction of the muscularis mucosae and spasm of the pylorus.

Satterthwaite (343) lists as prominent signs of adrenal insufficiency muscular asthenia, sensitiveness to cold, anorexia, weak cardiac action and pulse, hypotension, subnormal temperature, anemia, lowered metabolism, indigestion, constipation, psychasthenia, Sergeant's white line (in some cases), a dry skin, and lack of capacity for sustained effort. In such cases he has seen very satisfactory improvement following the use of dried adrenal extract, giving  $2\frac{1}{2}$  grain capsules three times daily, and adding  $\frac{1}{10}$  grain posterior lobe pituitary extract to supplement and sustain the action of the adrenal extract. He thinks that endocrine preparations are more effective when given in combination with one another. The pituitary usually provides an initial stimulation to activity of other preparations. He thinks that the beneficial effect upon the circulation is obtained by direct action of the glandular extracts on the myocardium and by stimulation of the cerebrospinal nerves, which govern the muscles of the heart.

*The "white line" of Sergent*

"La Ligne blanche surrenal," the white line of adrenal insufficiency, was first described by Sergent (344) in 1903. Since this time a considerable amount of literature of a conflicting nature has appeared concerning this phenomenon. As has already been noted here, there is increasing tendency in the recent literature to deny that the white line is a sign of adrenal insufficiency, a point of view shared even by Sergent himself (332). Sézary (345) concludes as the result of his studies that there is but one white line of the skin and that is the physiological one described by Marey in 1858. It is observed in both well and diseased persons. Whether isolated or associated with asthenia or arterial hypotension, this white line has no relation to adrenal insufficiency. Kay and Brock (346) studied 255 persons, including normals and patients showing a variety of diseases. On these persons numerous pharmacologic and other tests were performed. These authors conclude that the white line of Sergent is a local vasomotor reflex, resident in the skin and bearing no direct relationship to adrenal gland activity. Their reasons for this conclusion are: The line occurs independently of hypotension, fatigability and other signs of hypoadrenia. It persists in spite of persistent general manifestations of epinephrin administered subcutaneously. It shows a peculiar association with scarlet fever. The state of the vasomotor system which permits its best exhibition is found in young adults of either sex, and during the exanthem of scarlet fever. Discussing the value of the white line as a diagnostic aid, Maranon (347) says that acute adrenal insufficiency is characterized by hypotension, asthenia and tachycardia, symptoms similar to those of post-infectious myocarditis, diagnosis of which is impossible. The same difficulties are encountered when fulminating adrenal insufficiency manifests itself in meningitis, encephalitis or acute peritonitis. In these cases, where the characteristic skin pigmentation of chronic adrenal insufficiency is lacking, many observers have attached diagnostic significance to the white line. Maranon believes that this is not a symptom of a hypotensive state, but is, rather, a vasomotor phenomenon, indicating irritability of the vegetative system not allied to any determined disorder. It is not a basis for the diagnosis of obscure states

of adrenal insufficiency Wright (348) reviews the literature of the subject, and appends bibliography By the investigation of 100 healthy persons, he shows that the white line is a phenomenon occurring in a large proportion of healthy subjects It is without pathologic significance Various analogous physiologic responses are described He also concludes that the white line is not related to adrenal insufficiency nor to marked arterial hypotension It is produced by local emptying of the capillaries, due to the active contraction of some elements in their walls and is quite independent of the condition of the arterioles A nervous mechanism of the nature of an axon reflex may be involved Vincent (349) refers to the work of various observers, who have found the white line in various normal persons, and in various pathologic conditions not related to adrenal insufficiency During and after the war, various observers studied cases of irritable heart, or effort syndrome, in soldiers The white line was very commonly found in such cases Vincent draws the important conclusion from his studies, and from the study of the literature, that it is premature to recognize clinically a condition of "mild" adrenal insufficiency (of which until recently the Sergeant white line was considered diagnostic), until "our knowledge of the part played by the adrenals in the normal body economy is considerably extended"

*Addison's disease* Hanns (350) reports a case of Addison's disease with little pigmentation, relatively moderate asthenia and very great hypotension Abdominal palpation revealed a tumor, which autopsy showed to the adrenal capsule, increased in volume by tuberculous infiltration In this case there had been a series of accessory symptoms contraction of thigh muscles, uneven pupillary movement, ocular hypotonia, decrease of blood sugar, vasomotor disturbances in the fingers The author considers these phenomena to be of the same significance as the white line of Sergeant They are explained by vasomotor hyperexcitability due to defective functioning of the sympathetic Kraus (351) reports a case of Addison's disease in which autopsy showed tuberculosis of the adrenals, and marked atrophy of the pancreas He believes that such findings tend to support the theory of Falta, that there exists an antagonism of adrenal and pancreas

*Adrenalectomy* Peiper (352) in a discussion of the treatment of

Addison's disease recommends roentgen-ray examination of the kidney region after insufflation of oxygen into the bed of the kidney. He advocates removal when the adrenal capsule is the seat of a unilateral tuberculous process. In two cases of arterial *hypertension* Stephan and Florcken (353) did ablations of one adrenal. The only immediate result was a fall in the number of erythrocytes. Later on both patients showed increased skin pigmentation. In one case, in which the adrenals were exposed to X-ray, autopsy showed a reduction in size of the cortex. The chromaffin system was not altered. Crile (354) discusses his experience with surgery of the glands of internal secretion. He reports 21 adrenalectomies, in cases of epilepsy, neurasthenia, cardiovascular lesions and Raynaud's disease. His results were doubtful in epilepsy and neurasthenia, and negative in cardiovascular disease and Raynauds. No adrenalectomies for Addison's disease are reported. He believes that adrenal transplantation might perhaps be of benefit in this condition.

### *The pituitary gland*

It has been known for some time that certain types of dyspituitarism, notably certain types of hypopituitarism, are associated with low blood pressure. In the light of recent studies by Krogh and others, indicating that the pituitary hormone has to do with the maintenance of arterial pressure, largely through its action on the capillaries, this clinically established fact finds an explanation.

The association of infantilism with hypotension has already been noted (see that section). It is probably true that many cases of infantilism are due to mixed glandular insufficiencies, but it seems certain that certain types of infantilism are primarily hypophyseal in origin.

In those forms of hypopituitarism which manifest themselves in early adult life, asthenia and hypotension are also outstanding features. Cushing emphasizes the fact that in some of these cases the malady is a polyglandular one and that the adrenals and thyroid may also be implicated. The encouraging results which have followed the long continued administration of combined glandular extracts in such cases is also significant as to the etiology. Adiposis dolorosa and adiposo-genital dystrophy are generally considered to be due to

posterior hypophyseal lobe deficiency In both of these there is associated asthenia and hypotension

In general terms, it seems justifiable to say that as a rule hypopituitarism is associated with hypotension Cushing has however noted that there are exceptions, for blood pressure may be normal or even high in certain cases

### *The gonads*

The association of *hypertension* with the menopause has been observed and confirmed by so many observers, that the term menopause-hypertension is now in common clinical use The assumption is made that the internal secretion of the ovary has to do with the maintenance of blood pressure at or near normal levels This influence is diminished or removed at or shortly after the menopause, and hypertension ensues It has also been noted that substitution therapy, with ovarian extract, is of value, not only for the relief of the nervous symptoms of the menopause, but also for the relief of the hypertension Lowenthal (357) says that ovarian secretion increases vagus tone, and produces local vasoconstriction On the other hand, he says, the internal secretion of the testis produces changes of blood pressure only indirectly, by increasing the tone of the sympathetic system Strassmann (358) found an average increase of 20 mm Hg, in the blood pressure of women in the menopause, or with uterine myomata In 15 to 20 per cent of the former group, and in 40 per cent of the latter, the result of the persistent hypertension is cardiac enlargement Frequent uterine hemorrhages tend to lower the blood pressure Enucleation of the myomata did not influence it. Ovariectomy is followed at first by a lowering of the blood pressure, depending upon the gravity of the operation Later on the pressure rises (average 32 mm. systolic, 15 mm. diastolic) in women who had been previously menstruating Roentgen amenorrhoea after an ovarian dose produces no hypertension, probably because the internal secretion of the ovaries continues Only the deep irradiation in malignant tumors raises the blood pressure and causes cardiac enlargement Similar views are expressed by Cotte (359) He finds that ovariectomy is very likely to cause a rise of arterial pressure In 52 patients whose ovaries had been removed for various causes,

36 showed hypertension at the end of three to six months. Such hypertension was always more marked in patients whose blood pressure had been relatively high before operation, and in patients who had uterine fibro-myomata. In young women, on the other hand, conservation of an ovary usually tends to check hypertension. Sterilization, or the induction of the menopause by radiation, does not cause elevation of the arterial pressure.

*Hypotension due to pluriglandular disturbances*

Hart (360) has made a careful study of the literature on constitution and disposition, basing his conclusions on a study of nearly 2000 articles. He points out that disharmony in the endocrine system plays an important part in the formation of types of constitution. He adds that it is exceedingly difficult to decide whether certain disorders involving the endocrine system are to be regarded as inherited or acquired disorders. Thus he is not sure that status lymphaticus is a constitutional hyperplasia of the lymphatic system. It is more likely a secondary form of reaction following an internal or an external lesion. Infantilism, of which there is no universal type, is the result of continued arrest of an organ or body part in a transient phase, and is probably connected with the endocrine system. Disturbances of the endocrine organs can be coordinated with all other organs. Disorders of the ductless glands may predominate. The ductless glands alone may be affected. In *asthenia universalis* the circulatory system plays no etiological rôle. The condition is due to general functional weakness, to a lack of energy in normal development and to the histological (and functional?) state of the tissues and organs. There is direct relationship between this condition and the endocrine system. Hammett (361) has made a very interesting study of interglandular associations. He points out that if it be true that the glands are interrelated, it is obvious that any disturbance of the normal balance of the system, either by disease or by design, would give an end result expressing the total disharmony, rather than the direct response of individual structures to a given stimulus. The experimental studies were made on normal rats, using the statistical method of partial correlation as the analytical procedure, and the weights of the thyroid, thymus, adrenals, pancreas,

gonads and hypophysis of male and female adult albino rats, as raw data Hammett states definitely that absence of weight correlation cannot, of itself, be taken as indicating absence of specific functional relationship. He has shown that several of the pairs of ductless glands exhibit no specific weight association whatever. There is also indirect, suggestive evidence to show that no functional correlation exists in such cases. The evidence collected by Hammett, having a possible relation with hypotension is as follows. There is apparently a definite thyroid-adrenal relation, and this specificity establishes the hypothesis of Marine (362) and his coworkers on a firm basis.

Hammett finds that the adrenals are positively and specifically correlated with all the other glands of internal secretion, save the hypophysis, in both sexes. Thus adrenals and thyroid, adrenals and gonads, adrenals and thymus are functionally related.

Furthermore, while the studies showed that some of the incretory organs are not interrelated specifically as a group, some of the unrelated pairs may be considered as indirectly associated through the intervention of a third member. The major mediating influence in this indirect association emanates from the adrenals. These glands are apparently the pivotal organs upon which depend the interglandular associations. The adrenals are an integrating agency, binding together certain of the other incretory structures into an associative relationship. This influence is more general and more specific in the female than in the male. The degree of association is also closer in the former than in the latter. These facts taken in conjunction with the finding that the adrenal-ovary correlation is considerably greater in degree than the adrenal-testis, indicate that the adrenal domination of the endocrine system is more far reaching and more intensive in the female than in the male.

Discussing the relation of adrenal cortex to thyroid and thymus, Marine (363) finds that thyroidectomy hastens involution of the thymus. Gonadectomy delays this involution, but does not cause regeneration. Adrenalectomy not only delays involution of the thymus and lymphoid tissues, but also actually causes their regeneration. Thyroidectomy prevents this reaction, even after combined adrenalectomy and gonadectomy. Adrenalectomy plus gonadectomy is a more powerful stimulus for thymus and lymphoid regeneration.

than either of these influences alone. The combined effects of these two factors result in certain lymphoid and thymus hyperplasia in rabbits and rats, which persists until regeneration of accessory interrenal tissue corrects the physiologic effect. The syndrome thus experimentally produced resembles status lymphaticus and is believed to depend mainly on a partial loss of certain functions in the interrenal and sex glands rather than of the chromaffin tissue. The normal and abnormal lymphoid hyperplasias of infancy and childhood are believed to be manifestations of a functional underdevelopment of the interrenal and sex glands of varying intensity. The so-called lymphatic constitution which underlies or accompanies exophthalmic goitre and Addison's disease also appears to be dependent on a partial suppression of certain functions of the interrenal and sex glands.

Tokumitsu (364) discusses the relations of the adrenal cortex and its function. He maintains that the adrenal cortex is entirely independent of the medulla. Its function, indeed, is antagonistic to that of the latter and inhibits epinephrin secretion. The cortex has a synergistic action with the pancreas for carbohydrate metabolism. Atrophy of the cortex is seen in the majority of cases of diabetes. It is especially marked when pancreatic changes are slight in severe diabetes. Glycosuria is caused when a large part of the cortex is removed even when the pancreas is not degenerated. The cortex is functionally antagonistic to the thyroid. The thyroid hypertrophies when the adrenal atrophies. The adrenal cortex accelerates pancreatic secretion. The accelerating action is the same even after the vagus or sympathetic nerves are cut. Its action is independent of secretin. This accelerating substance in the cortex lowers the blood pressure. The cortex is vital for life, the adrenal medulla has no influence on life. The thyroid and the adrenal medulla are functionally synergistic. Thyroid extract accelerates epinephrin secretion. The anterior and posterior lobes of the hypophysis are antagonistic for epinephrin secretion.

*From the clinical point of view*, Billings (365) discusses glandular therapy. He stresses the fact that substitutional organotherapy is of practical value to a limited degree only. Deficiencies of thyroid gland secretion may be overcome partially or wholly by the use of thyroid gland or thyroxin. Insulin aids and restores carbohydrate



metabolism, in conditions due to deficiency of the internal secretion of the pancreas. On the other hand, pituitary extract and epinephrin must be considered as pharmacodynamic preparations, because, up to the present time, the various preparations of the hypophysis and adrenals do not appear to take the place of the glands themselves, fully. With the exception of thyroxin and insulin, the use of preparations of other glands of internal secretion, hypodermically or intravenously, has not afforded uniform and consistent results that may be definitely ascribed to the specific effects of the internal secretions of the glands. Also, it must be remembered that the possible good effects of glandular extracts given hypodermically or intravenously may be masked by the reaction of the body to the foreign protein thus administered. Substitution organotherapy is embarrassed, also, by the difficulties attending the recognition and interpretation of the signs and symptoms due to the deficiency of secretion of a single gland. These difficulties are intensified in the case of syndromes due to pluriglandular deficiencies. Billings insists, and rightly, that the medical profession, holding, as it does, a position of trust to the public, should refuse to patronize and support those manufacturers of glandular products who publish statements of their therapeutic value without the support of established physiological and clinical facts. Asher (366) also discusses the difficulties of a scientific foundation for organotherapy. He avers that the conceptions of hypofunction and hyperfunction, are, even in the best studied instances (thyroid), to a large degree, artificial constructions. In other cases, as of excessive production of epinephrin or of pancreatic secretion, such assumptions are, so far, merely speculations. He points out that it makes a difference whether the action of a hormone increases in a simple proportion to the amount injected, or in a curve which reduces the interval between the threshold and the maximum of action. The matter is further complicated by changes in action which follow small and large doses of extracts epinephrin for instance. He points out that he (as well as others) produced in animals the extreme weakness of Addison's disease. Yet organotherapy fails in this disease. (There is however some evidence that organotherapy is of some value in Addison's disease. See that section.) None the less it is well that there should be voices raised in protest of what Abel has rightly

termed "the stampede to the pluriglandular gold fields" Howland (367) has put it very well in his discussion of endocrine therapy in infancy and childhood. He says that the conclusion is forced upon us, and it is a conclusion to which physiologists and pharmacologists will subscribe, that if we use single extracts in pediatrics we are limited to the treatment of two conditions—thyroid deficiency and diabetes. Pluriglandular therapy has come into being on the supposition that, not infrequently, there is a disordered activity of several glands, a failure of coordination among them. For the belief that numerous glands may be affected in such ways as to produce various clinical syndromes, there is no pathologic proof available. Neither is there chemical or physiologic *proof* of the existence of such conditions. The fact that gradual improvement follows the administration of a heterogeneous mixture of gland extracts is not sufficient evidence to prove that a gland or group of glands, in dysfunction, is the cause of a clinical picture. One has a right to demand a striking and almost immediate change. One must also demand pathologic, physiologic or chemical evidence. Howland feels that the clinician of the present day is in danger of losing his clinical sense and his critical judgment.

Sézary (368) discusses asthenias of endocrine origin. He points out that asthenia is common to many diseases of totally different origin, and adds that an unfortunate tendency to blame the endocrine glands for every symptom is becoming prevalent. Although asthenia is doubtless the most frequent symptom of endocrine disturbances, and characteristic of Addison's disease, in which histologic examination rarely fails to show adrenal lesions, anatomic findings do not support the conclusion that the asthenia of every endocrine syndrome is caused solely by adrenal insufficiency. Sézary recognizes two distinct types of asthenia, both of endocrine origin. The first is due to adrenal lesions. It is associated with muscular weakness and extreme fatigability. It occurs in Addison's disease and in adrenalectomized animals. Myasthenia should be the term of choice here, as the muscles themselves become exhausted and the symptoms correspond with the disease of that name (Erb and Goldflam's myasthenia). The second type does not furnish evidence of adrenal involvement at autopsy. Asthenia is present, but there is no increased muscular fatigability. These types can be distinguished by the

dynamometer The rapid muscular exhaustion of adrenal insufficiency gives a curve with a sudden drop. The muscular weakness of other asthenic conditions shows a slowly declining curve, similar to that of muscular fatigue in normal persons. Erb and Goldflam's bulbar asthenia is characterized by weakness of the oculomotor, facial and cervical muscles Asthenia of adrenal origin does not show any predilection for muscles innervated by the cranial nerves and is not followed by paralysis Therapeutically the non-adrenal types of asthenia are at times greatly benefited by the use of other glandular extracts, especially thyroid extract, and such cases are reported Blumgarten (369) says that hypotension, unassociated with such conditions as anemia, tuberculosis, hemorrhage, etc., is usually merely an individual marking of an endocrine disturbance, such as acromegaly, or Froehlich's syndrome or adrenal insufficiency. He has not obtained much benefit from the use of glandular extracts in such types of hypotension, though he recommends their trial Hoxie (370) discusses endocrine therapy in cases of low blood pressure He suggests as a working classification of types of hypotension (excluding such temporary hypotension as accompanies shock).

(a) Infections: acute, chronic, focal.

(b) Exhaustions. nervous, physical

(c) Congenital status lymphaticus, status hyoplasticus.

The congenital types, he says, do not offer "even theoretical encouragement for the administration of glandular extracts"

In the infectious group, the blood pressure is a fair index of the body's success in its conflict with the infective agent or toxin In both acute and chronic infections, the blood pressure begins to rise as soon as the tissues win out Indeed hypertension may follow a long incidence of low blood pressure, because the high blood pressure and hardened arteries constitute the body's defense against the depressant effect of the toxins

The most persistent form of low blood pressure in this group is that due to some form of focal infection: tonsil, sinus, gall bladder, etc. Here the vasomotor tone of the body has been depressed for weeks or months In the presence of a persistent low blood pressure one should suspect the presence of focal infection Hypotension, due to exhaustion, is encountered in men subjected to long mental strain

The tired business man affords a good example. During the war, many instances were found in soldiers at the front.

The question is whether the endocrine hormones are the link in the chain between the causal infection or exhaustion, and the resulting lowered vasomotor tone and consequent hypotension, or whether the cause acts directly through disturbance of cell nutrition. If, for instance, the existence of a persistent focal infection has lowered the blood pressure, and if this has occurred because the body has been deprived of a needed hormone, it should be possible, by administering the hormone, to raise vasomotor tone and pressure, even while the infection persists. Or if the body be exhausted, substitution therapy should be effective in raising or maintaining tone before the exhaustion has disappeared. Such reasoning has been the basis for the widespread use of glandular extracts. As a matter of fact, says Hoxie, we are reaching the conclusion that depressed vasomotor tone and consequent hypotension is not due to the exhaustion of any one gland, or of a group of glands, but is due to "general nutritional causes" in which the hormones are only one factor. The use of such endocrine products symptomatically is therefore uncertain, and hardly possesses great superiority over other vasomotor stimulants of vegetable origin. One prime requisite in the treatment of low blood pressure is rest, rest of both mind and body.

Lisser (371), in an admirable paper, discusses the present achievements and future prospects of organotherapy. In his discussion of plurglandular therapy he proceeds to examine what he aptly terms the "plurglandular three-ringed circus." He grants that functional upheaval in any one gland does not ordinarily permit of normal function in the remainder, but frequently involves one or more or them in its tribulations. But, as he says, "in the enthusiasm for roping these glands together, a veritable jumble of knots has been tied that is difficult to untangle." If it be conceded that disease of one gland will produce disturbed function in one or more other glands, it is none the less true that restitution of the first gland to normal function will restore the remainder to normal function. And he offers some experimental proof for this contention. As Lisser sees the future of organotherapy, progress will depend upon carefully planned, united efforts of physiologists, chemists, pharmacologists, pathologists and

clinicians And he points out, in conclusion, that in such studies there must be neither ignorant credulity nor cynical intolerance "In endocrinology we have had too much of both "

#### GENERAL SUMMARY

Study of the literature concerning hypotension, covering both experimental and clinical observation, convinces one that there are many gaps in our knowledge of the subject Low blood pressure is a symptom or manifestation of an abnormal bodily state, rather than a disease itself It seems to be clearly established that in many persons, however, low blood pressure may be compatible with perfect health, that such hypotensives may even possess great bodily vigor

The complexity of the factors entering into the maintenance of normal blood pressure makes the determination of the causes of low blood pressure more difficult No single cause can be assigned for all types of hypotension. A rational procedure would predicate the discussion of types of hypotension in terms of malfunction of one, or of several, of these maintaining factors But it is just here that difficulty arises The interplay of the several factors, under normal conditions, is both close and complicated Structural change, disturbed nervous and chemical influences, act upon body parts and systems in such a way as to induce malfunction And the resulting pathological physiology becomes exceedingly difficult to explain There is a lack of agreement between clinicians, on the one hand, and physiologists and biochemists, on the other Clinical observation has shown, for instance, that marked hypotension occurs in certain conditions suggesting malfunction of the endocrine system Adrenal insufficiency is a case in point Persons with so-called adrenal insufficiency show very marked hypotension Post-mortem examination in these cases shows definite anatomic lesions of the adrenals And yet the establishment of direct causal relation, resting upon the sure footing of established knowledge of physiologic or biochemic fact, is very difficult Indeed, at times, it is almost impossible

In attempting to summarize existing views concerning various types of hypotension, it is therefore necessary to be conservative Certain facts have been clearly established With reference to other moot points, there is, in many instances, divergence of opinion Hy-

potheses have been advanced to explain certain other phenomena of hypotension, which cannot be said to rest upon a basis of established fact. And finally, certain phases of hypotension are as yet totally unexplained.

In the following summary the attempt is made to give facts and theories as such, and to point out that certain manifestations of hypotension, clinically recognizable, lack, as yet, a physiologic, biochemic, or pathologic-physiologic explanation.

*Blood pressure in the newly born* The average systolic blood pressure at birth is about 50 mm Hg, average diastolic 40 mm Hg. The blood pressure, which varies with the weight of the infant, rises steadily during the first days of life, so that by the tenth day in normal infants it averages about 80 mm Hg.

*Blood pressure in childhood* Pressure levels, both systolic and diastolic are lower in childhood than in adult life. Up to 10 years the average systolic is about 90 to 100 mm, slightly higher in boys than in girls. Up to puberty, the increase in systolic pressure is slight, but after puberty the gradient of rise shows an acceleration. Adult levels are reached at about eighteen years of age.

*Normal blood pressure in adult life* Two methods of study have been used by observers in attempting to determine norms of blood pressure: (a) Single estimations of blood pressure on large numbers of persons, (b) frequently repeated observations of the same persons, on much smaller groups. It is obvious that intensive studies of smaller numbers of persons, by repeated examinations under carefully ascertained and controlled conditions, give more precise results than do single examinations. Both methods have a rightful place in statistical studies.

The average systolic pressure is slightly higher at ages 18 to 21 years than it is later. In men the drop in pressure occurs from the ages 17 to 21. Normally, thereafter, systolic pressure tends to remain approximately constant up to the age of 50 years. In women the pressure drops from the years 17 to 25. Women show a rise after the twentieth-fifth year and a more marked one after the fortieth year. Hypertension, that is, systolic pressure over 120 mm, is very common among younger men. About 45 per cent of one large series had systolic pressures over 130 mm. Marked variations in the systolic

pressures of healthy young men have been noted by various observers

Racial, environmental and climatic conditions may change the normal average of blood pressure in young adults. Studies of the blood pressures of normal, healthy, vigorous young Chinese and Filipinos have given figures lower, by 10 to 20 mm, than the generally accepted averages for European and American whites

*The incidence of hypotension in normal, healthy whites*

Statistical studies made by the medical directors of a group of large American insurance companies showed that hypotensives are very good insurance risks. One company reports the records of 3389 persons, ages 16 to 60, accepted for insurance, all of whom had systolic pressures of 100 mm or less. Mortality of this group was just 35 per cent of the expected mortality, while the company's general mortality was 80 per cent of the expectancy (American men table)

Various statistical studies on normal persons have shown an incidence of hypotension of 2 to 3 per cent of the persons studied

*Blood pressure during sleep* Both systolic and diastolic pressures fall during sleep, the fall paralleling the depth of the sleep. Interesting studies have been made of the blood pressure during sound dreamless sleep, and disturbed sleep with dreaming. In the latter type sharp rises of blood pressure occur. Dreams of motor effort may thus throw a marked strain on the circulatory system in patients with cardiovascular lesions. These observations offer an explanation of the clinically attested fact, that patients with cardiovascular lesions awake in the morning after fitful disturbed sleep, with exaggerations of their symptoms of subjective distress. Subjectively the disturbed sleep with its raised blood pressure causes much after discomfort. Objectively the hypertension, often repeated, becomes a source of real danger.

*Blood pressure and muscular exercise* It is now generally agreed that no sweeping conclusions may be safely drawn as to the state of myocardial efficiency, based upon mathematical formulae as to time of return of pressure and heart rate figures after limited exercise. Measurements *during* the period of exertion constitute the only valid evidence as to the actual rise of blood pressure. In most studies of

the arterial response to exercise, little attention has been paid to the venous pressure. Furthermore it has been shown that the extent and course of the response of blood pressure to exercise varies a great deal in different types and degrees of muscular activity. The questions of the type of effort, i. e., short and maximal, or longer continued milder efforts, the degree of mental concentration necessary, and the state of fitness and training of the individuals, must all be considered.

For detailed summaries of various investigations, see the section itself.

*Blood pressure and body weight* In a study of 150,419 men coming up for life insurance, and grouped by ages and build, it was found that there is a definite relation between blood pressure and body weight at all ages. The effects of obesity in increasing blood pressure are distinctly pronounced. These findings have been corroborated by other observers. In several other series it was found that there was a higher percentage of hypertension cases among overweights than in persons of normal weight.

#### *The factors entering into the maintenance of blood pressure*

The factors which maintain blood pressure are (a) the force of the cardiac contraction, (b) the condition of the vessel walls, (c) the peripheral resistance to the blood stream, (d) the blood volume and the physical state of the blood itself, its viscosity, etc. These factors are *not* of equal importance. The condition of the myocardium (a), determines the force of cardiac contraction. Certain types of hypotension are due to a weakened *vis a tergo*. The physical state of the conducting vascular system (b) probably plays little rôle. Flaccid and toneless muscle fibers in blood vessel walls, such as are found subsequent to the toxemia of acute infections, may temporarily lower blood pressure. The factor of peripheral resistance (c) is of very great importance. It is probably the most important single factor, both in the maintenance of normal pressure and in the production of hypotension. The arterioles and capillaries are normally held in a state of tonic contraction by impulses delivered from the vasomotor center. Peripheral constriction is thus subject to the ebb and flow of vasomotor impulses. The endocrine system works in conjunction with the vasomotor system, exerting either a pressor or



depressor action on vasomotor function. Endocrine dysfunction therefore plays a definite rôle in the production of hypotension. The factor of peripheral resistance presents many phases, some of them deviously interrelated. It is in the interpretation of hypotension associated with changed peripheral resistance that our greatest difficulties lie. Change in blood volume (d) is of considerable importance in the production of certain types of *acute* hypotension. Reduction of blood volume is probably the determining factor in the production of wound or surgical shock. In conditions where there is great loss of body fluids, with consequent diminution of blood volume, acute hypotension is apt to supervene. Relative diminution of blood volume, due to capillary stasis, so that the actual volume of circulatory blood is greatly diminished, is also of much importance in the production of low blood pressure. Increased viscosity of the blood, in conjunction with other factors, also plays a rôle in the production of certain acute hypotensions.

*Types of hypotension* Low blood pressure may be either a temporary or a persistent phenomenon. Acute hypotension is part and parcel of traumatic, anaphylactic, and anesthetic shock. It occurs in certain of the acute infectious diseases. It may be the result of certain drug intoxications.

Persistent hypotension occurs in association with certain chronic infectious diseases and cachectic states. It is found in such diatheses as infantilism, status lymphaticus, myxedema and myasthenia. Lesions of the circulatory system, particularly of the myocardium, may produce either temporary or persistent hypotension. Certain types of body habitus are associated with hypotension. Essential hypotension constitutes a fairly definite syndrome, whose real nature is as yet not definitely understood. Chronic hypotension occurs in conditions of endocrine gland dysfunction, especially of the adrenals, hypophysis, gonads, and thyroid.

The correct evaluation of the rôle of the factors that maintain blood pressure in the production of these types of hypotension is a matter of much difficulty at times. This is in part due to the fact that the hypotension may not be due to malfunction of one factor, but to maladjustment of the interplay of several. It must also be remembered that the amplitude of blood pressure variation, consistent-

ent with perfect health, is very great. Also that a very appreciable percentage of apparently healthy persons have persistent hypotension.

*Anaphylactic shock* The fall of blood pressure in anaphylactic shock is due to dilatation and congestion of the large venous trunks of the splanchnic area, with coincident medullary anemia. The splanchnic congestion produces a lack of vasomotor tone with consequent disturbance of the blood volume.

*Traumatic shock* The factors entering into the production of wound shock may be divided into initiating and sustaining factors, accounting, respectively, for primary and secondary shock. Primary shock, which is of much less importance than secondary shock, is probably most readily accounted for on the basis of some disturbance of the nervous system. It is probable, that, as a consequence of wounding, there is a reflex dilation of blood vessels similar to that which occurs in fainting. So far as secondary shock is concerned recent research has shown that there is no convincing evidence that the heart muscle itself, or the nervous agencies controlling the heart, exhibit any changes in shock to justify the assumption that they are primary factors in the lowering of blood pressure. Ordinarily, in shock, exhaustion of the vasomotor center (or even weakening of its tonic activity) is not primarily the cause of the low blood pressure.

The theory of shock which has the strongest support in clinical observation, and in laboratory experiment, is that of a toxic factor, operating to cause an increased permeability of the capillary walls, and a consequent reduction of blood volume by escape of plasma into the tissues. After sufficient time has elapsed, infection may be an added factor in inducing persistent hypotension. The similarity between experimental histamin shock and actual wound shock is noteworthy. Although proof is still lacking that a substance, histamin-like in character, is actually given off when the tissues are severely damaged, there are many reasons for thinking that the supposition has a high degree of probability. The evidence collected, while not absolutely conclusive, points very strongly to the conclusion that the toxic factor in the production of wound shock is either histamin or some histamin like body.

In addition to the toxic agents, hemorrhage, cold, exposure, and anesthesia after hemorrhage may be factors in the production of the

marked hypotension. Also, in secondary shock, there is marked relaxation of the capillaries and injury to the capillary endothelium. A series of vicious circles may thus be set up to prolong or increase the hypotension.

*Surgical shock* Like wound shock, surgical shock may be divided into primary and secondary manifestations. Primary surgical shock is probably due to disturbance of the nervous system—anxiety, dread of the operation, etc. Ordinarily this type of shock is not serious, but primary shock may be fatal. Such cases are reported. Speaking generally however, the term surgical shock is used to denote the manifestations of secondary shock, accompanying or following surgical operations. Among the factors tending to favor the occurrence of surgical shock may be mentioned: hemorrhages, toxic agents from infection, loss of body fluids from various causes, tissue trauma, handling of the abdominal viscera and anesthesia itself. In the production of the surgical shock there may be the interplay of several causative factors.

The diminution of the volume of blood in circulation during or after operations is the most potent factor in the production of the low blood pressure which accompanies surgical shock. The degree of diminution of blood volume in shock may be estimated from the fact that plasma volume is reduced 10 to 20 per cent in cases of mild shock, and from 50 to 60 per cent in severe cases. Moderate hemorrhage alone does not necessarily produce shock. Experimentally it has been shown that reduction in blood volume from hemorrhage exceeding 30 per cent, causes a marked drop in blood pressure. Tissue trauma during operation may liberate toxic material which tends to produce shock. As to the nature of such toxic material, there is, as yet, no definite knowledge, but such effects can be paralleled by the injection of histamin. The anesthesia itself heightens the shock-producing effects of such toxic material. Prolonged anesthesia produces, in many instances, marked dilatation of the peripheral vessels. There is direct relationship between vasomotor control and blood pressure. The end result of ether depression may be marked loss of vasomotor function.

Visceral trauma, especially of the abdominal viscera, produces dilatation of the splanchnic arterioles, capillaries and venules, with

resulting hypotension Trauma to the viscera may thus produce shock, due to loss of circulating fluid in the traumatized areas, mainly brought about by a local peripheral mechanism McKesson's law is generally regarded as a reliable index a pulse rate of 100 and ascending, with progressive falling blood pressure reaching 80 mm or less, and a pulse pressure of 20 mm or less, if continued over thirty minutes, invariably ends in shock The longer the low systolic pressure persists during operation, the less is the likelihood of recovery In such cases death may not occur till the second or third day after operation

*Blood pressure and the anesthetic itself* All anesthetics in common use cause a fall of blood pressure, if the administration be continued more than a few minutes Chloroform causes the earliest and most abrupt fall The drop under ether comes later and is less marked Nitrous oxide-oxygen causes very little drop in pressure, unless administration be prolonged over two hours Anesthesia favors the occurrence of shock Chloroform has a greater tendency than ether Nitrous oxide-oxygen has less tendency than either of the others to produce shock

*Local anesthesia* Lowering of blood pressure during operations under local anesthesia is not due to the local anesthetic, as a rule, but rather to operative trauma and length of operation The advisability of supplementing the local anesthesia with a few whiffs of a general anesthetic at the moment of greatest injury to the tissues is stressed This holds good particularly when it is not certain that all centripetal nerve tracts have been blocked

*Spinal anesthesia* During the war it was found that operations under spinal anesthesia on soldiers suffering from shock could not be done with safety, because of the further drop in blood pressure induced Even in civil practice it is found that a drop in blood pressure accompanies each spinal anesthesia The drop may be so great as to be fatal The low point in pressure is usually reached ten minutes after induction of spinal anesthesia After fifteen minutes one is working away from the danger point Epinephrin, given intravenously, is often of value in marked hypotension after spinal anesthesia

*Treatment of wound and surgical shock*

*Wound shock* Primary shock requires rest and quiet. Prophylaxis of secondary shock is of much importance. A differentiation of cases of shock into three groups is of value from a prognostic as well as a therapeutic point of view. Group 1—the compensated group. Here the blood volume is not reduced below 80 per cent of the normal. The plasma reduction is even less, plasma volume being 85 to 90 per cent of the normal. Such cases recover if kept warm, and given fluids by rectum. In group 2, the partially compensated cases, the blood volume and plasma volume are reduced to 65 to 75 per cent. Transfusion is needed here, to be repeated within a few hours if the plasma volume does not rise promptly. In group 3, the uncompensated cases, the blood volume is below 65 per cent and the blood concentration greatly increased. The outlook is bad, because here the transfused fluid readily leaves the vessels, causing pulmonary and tissue edema. Here repeated transfusions are necessary. Fluid added by transfusion makes good the blood lost by stagnation, etc., and maintains normal pressure for a time sufficient to permit the organism to destroy the toxic bodies. Special indications include the prevention of hemorrhage if possible. Tourniquets are to be avoided if possible. If a tourniquet must be used, it should be set close above the traumatized tissues and left in place until after amputation, to prevent absorption of toxic material from the injured tissues.

It is of great importance to conserve the body heat left, and, if possible, to restore that which is lost.

Drug treatment in secondary wound shock is of very little avail. The temporary raising of the blood pressure by the use of epinephrin or pituitrin, cannot improve the volume flow in the capillaries. This can only be done by increasing the blood volume. The best method to increase blood volume is to increase the amount of circulating fluid. The simplest way to do this would be to give fluids by mouth. In well developed shock, however, vomiting is apt to occur, so that fluid given by mouth cannot be retained. In mild cases, fluid given by rectum is sometimes retained, and if so is of value. Salines given subcutaneously are of real value, partly as a prophylactic measure (as

in operations), and partly as a therapeutic aid. Transfusion is the best method for increasing blood volume in cases of severe shock. Various solutions have been used. Salines have been used extensively. During the war, the English surgeons used gum acacia solutions very extensively. There has been much discussion as to the value of the gum solutions. The preponderance of evidence would indicate that, properly prepared and administered, they act very well in shock.

There is no question of the value of blood transfusions in shock. Blood is probably preferable to any indifferent fluid. Given under proper precautions, it is the best therapeutic agent in the treatment of severe secondary wound shock.

*Surgical shock.* Operations on patients with marked hypotension should be delayed if possible, until means have been taken to raise the blood pressure. Operative procedure should be as short as is consistent with thoroughness. There should be no waste of time. Every effort should be made to avoid unnecessary hemorrhage. Chilling of the patient must be avoided. Nitrous oxide-oxygen should be the anesthetic of choice. Transfusion of gum solution or of blood should be employed if the pressure remains near the danger limit.

In operations on patients with arteriosclerosis, special attention should be paid to the avoidance of sudden drops in blood pressure. This holds good especially in cases of cardiac decompensation.

The loss of body fluids is to be prevented when possible. Where such loss has occurred, the replacement of fluids by one of the methods generally used is advocated.

The patient's position on the table merits special attention in such cases. Cerebral anemia is lessened by the Trendelenburg position.

The treatment of actual surgical shock follows the accepted standards for treatment of wound shock.

*Hypotension in acute infectious diseases.* Most of the acute infectious diseases are accompanied by hypotension, the drop in pressure being more marked in some than in others.

During the height of fever, blood flow, especially in the capillaries, is slower than in health. Such relative capillary stasis would be a factor in the production of febrile hypotension. The increased body temperature in infection is one factor in the hypotension. The weak-

ened heart action due to cloudy swelling or degeneration of the heart muscle, in certain infections, is another. Loss of splanchnic tone due in part to toxemia, in part to weakened arterial musculature, is another. This loss of vasomotor tone explains many of the hypotensions seen in post-infectious asthenias.

*Typhoid fever.* Apart from certain complications, the course of the blood pressure in typhoid is progressively downward. One observer believes that the hypotension is in direct relation to the severity of the attack. With the advent of hemorrhage, the pressure usually drops very sharply. Such a drop in pressure is to be explained by diminution of blood volume. A sudden rise of pressure is usually found when perforation has occurred. It is supposed to be due to constriction of the splanchnic vessels. Involvement of the myocardium is the rule in typhoid, so that the cardiac factor is of prime importance. The vasomotor factor (vasomotor depression) doubtless also plays a rôle.

*Pneumonia.* Hypotension is the rule in pneumonia, but it is by no means always present, even in the severest cases. The hypotension is due to the toxemia and its effect on the vasomotor centers. Attention has been called, repeatedly, to the fact that death in pneumonia is frequently attended by the signs and symptoms of surgical shock. The degree of toxicity in a given case may be rated by the severity of these "shock" symptoms during life. The condition of the heart muscle itself is a factor in the production of hypotension in some cases of pneumonia. The recognition of this cardiac factor has led to the widespread practice of routine digitalization in the treatment of pneumonia.

Hypotension in pneumonia is due to a cardiac factor, a toxic vasomotor depression factor, or to a combination of both of these.

*Influenza.* Hypotension is the rule during the acute stage of influenza. The asthenia during the last pandemic reached very extreme degrees. The cardiac factor, the vasomotor factor and the reduction in blood volume all play rôles. The persistence of hypotension for a long time after the acute attack has subsided is to be attributed in many instances to myocardial involvement, but persistent lack of vasomotor tone also accounts for some of the long continued post-influenzal asthenias.

*Diphtheria* Marked hypotension is found in the more severe cases. In such cases there is a marked reduction in blood volume due to uneven distribution of the blood. The vasomotor depression cannot account altogether for all the cases of hypotension, because in many instances there is definite and marked myocardial involvement.

*Scarlet fever* Pressure variations in scarlet are not uniform and not remarkable. Where hypotension is found, it is due to vasodilation and left ventricular weakness, i e., a combination of the vasomotor and cardiac factors.

*Cholera* In the algid stage there is marked hypotension, with, as a rule, diminution in pulse pressure. Hypotension is due to direct reduction in blood volume, due to loss of plasma from the circulating blood. The viscosity of the blood is also increased. The use of intravenous saline injections, whose value has been repeatedly attested clinically, tends to restore the blood volume.

*Malaria* Hypotension is more common in chronic malarial cachexias than in acute forms. Clinically and experimentally, it has been shown that heavy infection may result in plugging of the capillaries with plasmodia, particularly the cerebral capillaries. Marked hypotension in chronic malaria may thus have a certain prognostic importance.

*Typhus fever* Hypotension is usually marked in typhus. The myocardial changes are as a rule not as marked in typhus as in typhoid. Toxic vasomotor depression is the probable basis of the hypotension in typhus.

*Trichinosis* Recent studies have shown that severe infestation with trichinae usually produces marked hypotension. This is, in all probability, of toxic myocardial origin.

*Tsutsugamushi disease (Japanese flood fever)* A recent monograph on this disease, endemic in certain parts of Japan, shows that its clinical picture to some extent resembles that of typhoid, with the addition of a generalized adenopathy. The heart, in fatal cases coming to autopsy, always shows marked cloudy swelling. The hypotension, which is constant, is doubtless due to myocardial weakness, the result of the toxemia induced by the bite of the insect which causes the disease.



*Hypotension in chronic diseases*

*Tuberculosis* In the advanced stage of the disease, with pronounced toxemia, marked hypotension is the rule. In the incipient stage however, there is no constant hypotension. Various investigators have found that the degree of hypotension stands in direct relation to the severity of the disease. Normal pressure, or *hypertension*, is usually regarded as a good prognostic sign. Hypotension in tuberculosis is probably the result of a toxic action on the vasomotor center. Cardiac degeneration or atrophy is a secondary factor. Some authors have believed that blood pressure estimations might be used as a check to determine the amount of exercise allowed the tuberculous patient. There has been some discussion of the effect of the establishment of artificial pneumothorax, in tuberculous patients, on the blood pressure. Studies are reported to show that the induction of artificial pneumothorax has no marked influence on blood pressure.

*Syphilis* The earlier view was that the hypotension sometimes found in the early stages was due to the aortitis. More recent studies have shown, however, that there is nothing characteristic in the blood pressure readings in the majority of cases of cardiovascular syphilis. Hypotension, when it does occur early, is, in all probability, due to the factor of myocardial degeneration. A form of syphilitic hypotension to which attention has been paid of late is that associated with syphilitic lesion of the adrenals. One author, in a study of the histologic lesions of the different organs in 90 autopsies on syphilitic persons, found lesions of the adrenals in 75 of the cases. Syphilis of the adrenals probably produces very marked hypotension. Addison's disease, however, apparently does *not* rest upon a luetic basis in many instances.

*Diabetes.* Diabetes, *per se*, apparently influences blood pressure very little. According to some investigators, the blood pressure in diabetes is slightly below normal until the age of thirty-five is reached. Thereafter the pressure rises above normal, and the interval between diabetic and normal persons widens as age advances. In a study of 500 cases of diabetes made since 1919, 35 (7 per cent) showed definite hypotension. The suggestion is made that the number of

cases of hypotension had become greater since undernutrition was introduced, and prior to treatment with insulin

*Addison's disease* Marked hypotension is one of the outstanding clinical features of Addison's disease, although, as has been shown recently, it is not invariably present. Pathologically, the principal lesion is tuberculosis of the adrenals. Syphilitic lesions of the adrenals have been found in a few instances. A considerable proportion of persons having Addison's disease show the characteristic features of the lymphatic or thymolymphatic constitution. Despite this knowledge it is, at the present time, impossible to explain with entire satisfaction the hypotension of the disease in terms of dysfunction of one or of several of the factors which ordinarily maintain normal blood pressure. Organotherapy has been tried for over twenty-five years in Addison's disease. The results have certainly not been uniformly good. Recently, the combination of forced substitution organotherapy, whole gland with the addition of epinephrin, has been made the subject of special study.

*Food deficiency diseases* The hypotension found in some of the food deficiency diseases is ordinarily not marked. It is suggested that in malnutrition and avitaminosis the hypotension may be due to adrenal dysfunction.

*Bronchial asthma* There is general agreement today that the underlying factor of primary bronchial asthma is protein sensitization of the individual. It is thus possible that the anaphylactic shock in asthma is due to a toxic split protein which, circulating in the blood, affects the autonomic nervous system. It is believed by some that imbalance of the endocrine system may also play a rôle, so that there may be produced some dysfunction of the autonomic nervous system. The hypotension which is commonly found, would, in either case, be due to lack of vasomotor tone.

*Focal infections* Focal infections arising from chronic inflammation of tonsils, teeth, accessory nasal sinuses, gall bladder, genitalia etc., are very frequently accompanied by marked hypotension. Such low pressure is, of course, apt to be persistent. It is even asserted that the most persistent types of hypotension belonging to the infectious group occur in cases of focal infection. The low blood pressure may even be a sign of diagnostic value. Such hypotension is

due to marked depression of vasomotor tone, though myocardial change may account for some cases of persistent hypotension in focal infection

*Non-infectious chronic arthritis* Certain cases of chronic arthritis appear to depend upon endocrinopathies, particularly on disorders of the thyroid. In addition to the joint symptoms, they show a low metabolic rate, generally lowered physical tone, bradycardia and hypotension. Such cases often improve remarkably under thyroid therapy, even though they are not typical myxedemas

*Anemia.* The hypotension from hemorrhage is due to reduction of blood volume. In anemias not due to hemorrhage there is often marked hypotension. In pernicious anemia systolic pressures of 80 to 60 mm are not unusual. The peripheral blood flow has been found to be much diminished in severe anemias. Such changes are regarded as a compensatory effort on the part of the peripheral mechanism to divert blood from the periphery to more vital organs. In this way the return of the blood to the heart and lungs is assisted. The relative peripheral stasis is one probable basis for the hypotension.

*Cachexia* In advanced cachexias hypotension is the rule and may become extreme. Deterioration in quantity and quality of the blood, anemia from the repeated hemorrhages which occur in some cases, and myocardial weakness, would, separately or together, explain the hypotension.

### *Hypotension in certain constitutional diatheses*

*Status lymphaticus* The hypotension in status lymphaticus is to be explained partly in the basis of the cardiovascular hypoplasia with its resultant diminution in driving power. It may also stand in relation with the hypoplasia of the chromaffin system which is, in all probability, part of this diathesis.

*Infantilism.* The Lorain type of infantilism is now considered to be due to toxemia, the result of disease in intrauterine life, or in early infancy. Its hypotension would thus be easily explained. In the Brissaud type there is lesion or dysfunction of one or more of the ductless glands. The hypophysis and thyroid are most commonly at fault, and the hypotension depends upon these glandular dystrophies.

*Myasthenia gravis* While it cannot be stated positively at this time that myasthenia is always dependent upon a lesion of the thymus, it seems established that there is a connection in a considerable proportion of the cases. Irradiation of the enlarged, or persistent thymus, with resulting involution of the gland, has been followed by marked improvement in the myasthenic symptoms, including the hypotension. In certain cases of myasthenia of the amyotrophic type, evidences of adrenal insufficiency have been found.

*Adiposis dolorosa* There is still no agreement as to the cause of this condition. Atrophy of the thyroid, pluriglandular dystrophies involving thyroid, hypophysis and adrenals, lesions of the gonads, have all been found and the symptom complex ascribed to them. In fifteen cases coming to autopsy, there was pluriglandular involvement in thirteen. It has been emphasized that many cases of endocrine adiposity begin as a uniglandular disorder. The hypotension stands in relation to the ductless gland lesion.

#### *Hypotension due to certain mechanical factors*

*Postural change* The change in position of the body from the recumbent to the erect position throws a definite strain on the organs of circulation, determined by the gravitation of the blood. Normally, on change from the recumbent to the standing position, the splanchnic vasomotor tone overcompensates the hydrostatic effects of gravity. In general, both men and women, on arising from a supine position, show a slight drop in systolic pressure, a slight rise in diastolic pressure and a rise in pulse rate. Excessive fall of systolic pressure shows weakness of vasomotor control. Excessive rise of diastolic pressure denotes vascular spasm and abnormal effort. Individuals in whom there is excessive gravitation of blood to the extremities and the splanchnic area on standing are the victims of physical weakness and nervous instability. Such individuals show marked hypotension. The various types of postural hypotension are considered, and three very unusual cases, with the authors' comments, are discussed in detail.

*Body habitus* The assumption that asthenia and hypotension are due to certain types of body habitus has been current for a long time. Medical literature has teemed with articles on dropped

stomach, ptotic intestinal viscera and the dangers resulting therefrom. Congenital and acquired forms have been described. Recently, various sets of careful studies have been made, which must convince an impartial reader that the drawing of sweeping conclusion as to fixed relations between body build and body function are, to say the least, hazardous. Even though it be admitted that the combination of constitutional asthenia, sagging of the viscera and weak circulation is rather frequently found, it is not proved that the body habitus itself is the cause of the symptoms, including the hypotension. The factors of myocardial weakness and loss of vasomotor tone must be taken into account. The explanation of malfunction of these factors is often found to bear no relation to the body habitus itself.

*Effects of exposure to high temperature upon circulation in man.* Low blood pressure in cases of heat exhaustion and certain of the milder cases of insolation is accompanied by the general picture of shock. Recent experimental study on the effects of high temperature on man has shown that there ensues marked dilatation of the peripheral vessels. The lack of high resistance in the peripheral vessels prevents the blood from returning to the heart, and the general picture of circulatory failure, and finally of shock, supervenes. The explanation of the hypotension is that there is relative diminution of the blood volume. Other factors may play contributing rôles.

*Variations in atmospheric pressure.* The remarkable adaptability of the normal human mechanism to changed and changing conditions of barometric pressure has been noted by various observers. Blood pressure studies at high altitudes have shown that there is a primary fall of arterial pressure, but it is not marked. The initial drops are more extensive in hypotensive individuals, than in those with ordinarily normal pressure. Recently, studies on blood pressure variations during aviation have been made. Where drops in pressure occur at high altitudes, return to normal pressure and disappearance of the phenomena of flight sickness disappear as soon as oxygen is inhaled. The influence of oxygen is still manifest at an altitude of 26,000 feet. Various new tests for aviators and statistical studies of blood pressure and other phenomena, are discussed.

*Action of tissue extracts on blood pressure.* It has been known for many years that various tissue extracts have a depressor effect on

blood pressure It has been shown that histamin is a widely distributed constituent of animal tissues, organ extracts and enzymatic products derived from animal or vegetable protein But it is probably not true that histamin is the only constituent of tissue extracts capable of lowering blood pressure

*Liver extract* Recently, renewed attempts have been made to find the active depressor substance in liver extract Several investigators have succeeded in producing extracts whose chemical and pharmacological properties are now being studied It would appear that the depressor substance in these extracts is non-protein in character It is not histamin and not cholin, as shown by careful chemical tests On experimental animals it has been found that marked drop in blood pressure follows the injection of the extract Overdose kills the animals in one to two minutes, without convulsions At autopsy the heart and lungs appear normal The blood seems to have collected in the larger vessels The effects of injection of liver extracts in human beings with hypertension are now being studied in several clinics Encouraging results are being reported, but so far merely the preliminary stage of the study has been reached

*Parathyroid extract* The later reports on the parathyroid hormone indicate that, in conformity with most other tissue extracts, the intravenous injection of purified parathyroid extract causes a slight fall in blood pressure The drop does not last long There is apparently some diminution of blood volume Subcutaneous injection of the extract does not produce a fall in pressure

*Insulin and blood pressure* There has been some discussion recently as to whether the injection of insulin tends to lower blood pressure directly In hypoglycemic conditions vasomotor phenomena are common Pallor or flushing, a sense of heat or of chilliness, and profuse sweating are present At lower levels of blood sugar, acute mental distress, mental disturbances, delirium and coma supervene In explanation of such manifestations it appears that the stimulus set up by the decrease of the circulating blood sugar may act on certain nerve centers, notably in the region of the pons and medulla There is also the possibility that the hypotension which follows the administration of large doses of insulin may act upon the cardiac factor in the maintenance of normal blood pressure The

reduction in the amount of carbohydrate available for utilization by the heart muscle, may so reduce its power that the asthenic picture supervenes

*Epinephrin and blood pressure* The rise of blood pressure which follows the intravenous injection of epinephrin is, for the most part, due to constriction of the vessels of the abdominal cavity. In addition, there is some direct action on the heart. Small doses accelerate heart rate and strengthen output. In large doses the acceleration may be excessive and may impair the heart efficiency. Clinically, one indication for the use of epinephrin is in cases of marked hypotension due to vasomotor weakness, without cardiac depression. Its action is more prompt after intravenous injection, slower but somewhat more prolonged, when given subcutaneously. In addition, it is of great value where local constriction of vessels is desired.

*Pituitary extract* Intravenous injection of pituitrin causes a rather slow rise in blood pressure. The rise is smaller and less abrupt than that which follows injection of epinephrin, but it is maintained longer. The rise in pressure is due to constriction of peripheral arterioles. Clinically, pituitary extract is of value in cases in which hypotension is due to loss of splanchnic vascular tone. Its long continued use in certain forms of dyspituitarism has, in many instances, been followed by marked improvement in the symptoms.

*Thyroid extract* Injected intravenously, thyroid extract produces a fall of blood pressure, but the action is not marked. Apparently thyroxin acts in the body as a catalyst. It merely increases the rate at which fundamental reactions are carried out. The thyroid apparatus has apparently been added to the animal organism in order to permit a greater range of flexibility of energy output than would exist without such a mechanism.

*Gonad extracts* The ovarian field can point to no such persistent and systematic work of hormone isolation as we have in the cases of the thyroid or the pancreas. From the point of view of blood pressure studies, it would appear that the ovary, during its period of functional activity, has a function in maintaining normal blood pressure in women. The very common occurrence of post-menopause hypertension, and the value of substitution organotherapy in relieving such hypertension, are matters of clinical knowledge. The exact

mechanism is not clear. In men it has been found that extirpation of the testes is followed by a fall of blood pressure. It has also been claimed that the presence of successful testicular grafts, in any part of the body of castrated men, will reestablish vascular tone.

### *The effects of certain drugs on blood pressure*

*The nitrite group* The nitrites lower blood pressure by their action on the vessels. Both arteries and veins dilate considerably under the action of the drugs. The vessels of the abdominal organs and the face are affected more than those of the extremities. The vasomotor center is not concerned in the widening of the vessels. The use of nitrites in hypertension is purely symptomatic medication. They are, essentially, emergency drugs. They are of value in cases of threatened apoplexy or cardiac failure from hypertension. After intracerebral vascular rupture has occurred, they are contraindicated. So also in marked arterial hypotension. They should not be used in the hypotension of acute febrile disease or in shock.

*Alcohol* One chief effect of alcohol on the circulation is vasodilatation. Very large quantities of alcohol cause a marked fall in blood pressure through weakening of the vasoconstrictor centers and the heart muscle. Alcohol produces a definitely unstable vascular tonus. It is not advisable as a stimulant in conditions of low blood pressure. In the vascular failure of the acute infections and in surgical shock it may be actually harmful.

*Iodides* Iodides are not vasodilators in the sense that the nitrites are. Where existing hypertension is lowered after prolonged use of iodides, the inference is that the hypertension was due to luetic aortitis or endarteritis.

*Chloral* In therapeutic doses, chloral has comparatively little effect on the circulation. The action of the heart in chloral poisoning resembles that of chloroform. Drugs of the chloral group should not be used to reduce blood pressure.

*Opium* The effect of opium on the circulation is not marked. The blood pressure does not change. The fall in pressure which follows its use in certain cases of angina, hypertension from broken compensation, etc., is due to its sedative effect on the nervous system. Morphine itself tends to dilate the coronary arteries, while papaverin



at times produces a drop in pressure from peripheral action on the vascular walls

*Watermelon seed* Attention has recently been directed to the depressor action of *cucurbita citrullus*, and its active principle cucurbitacin. The toxicity of the drug is very low. Its action is rather slow, but prolonged. The hypotension induced is due to capillary dilatation.

*Glucose* In certain cases of hypertension it has been found that the intravenous injection of small amounts of glucose produced a drop in blood pressure. This is due to capillary dilatation. Excellent results have been reported in the treatment of angina pectoris by repeated injections of glucose.

*Quinidin sulphate* Immediately after quinidin sulphate is injected intravenously (in experimental animals) the blood pressure falls. After the administration of quinidin the animal is much less sensitive to the action of epinephrin than before such administration. Large doses of quinidin probably depress the vascular sympathetic nerve endings. There is also capillary dilatation, and there is definite dilatation of the peripheral vessels. It is not probable that the drop in blood pressure after therapeutic doses is very marked.

*Mistletoe* reduces pressure by dilatation of the peripheral vessels.

*Salvarsan* In experimental animals, the intravenous injection of salvarsan produces a marked drop in blood pressure, due in part to direct action on the walls of arterioles and capillaries, in part to central action. In man, the degree of blood pressure reduction after neosalvarsan is never sufficiently great to endanger a normal circulatory mechanism. Where, however, marked hypotension exists from any cause, the injection of arsphenamins may have serious consequences.

*Cinchophen* A case of very marked drop in pressure after the use of one dose of cinchophen is reported. The general picture suggested a vasomotor depression.

*Digitalis* Digitalis has no uniform action on blood pressure. The older notion that hypertension contraindicates the use of digitalis is no longer current. Neither is there any definite evidence to support the view, formerly held, that digitalis causes coronary constriction.

*Pressor drugs* *Ephedrin* Ephedrin is the active principle of an

**Asiatic drug, Ma Huang** It has physiological effects similar to those of epinephrin and tyramin. Its action is more prolonged, however. It can be given by mouth or subcutaneously. After its administration systolic and diastolic pressure are raised and the heart rate is slowed. It acts through peripheral stimulation of the sympathetic nervous system. It is now being tried, apparently with good results, in several types of hypotension.

**Caffeine** In cardiac inefficiency caffeine causes a drop in blood pressure. It also has a direct dilator effect on the coronaries.

**Strychnin** Strychnin stimulates the vasomotor center directly. Its use in hypotension is justified on this basis. Its supposed value has probably been overestimated by clinicians.

**Atropin** Atropin increases the pulse rate by depression of the peripheral ends of the vagus. There is no evidence that the medullary vasomotor center is excited by atropin. Clinically the pressor effects of atropin are not marked. It is, however, a valuable remedy in the wet clammy stage of vascular collapse.

**Ammonium** Aromatic spirits of ammonia acts as a cardiac stimulant, though its effect is very transient. Its pressor effect comes from constriction of peripheral arterioles, induced by stimulation of the vasomotor center.

**Ergot** The bases of ergot are ergotoxin, tyramin and ergamin. The first two of these resemble epinephrin in some of their effects. Ergotoxin, injected intravenously, causes an abrupt rise of blood pressure due to its action on the peripheral vessels. Clinically, ergot is of comparatively little value as a means to restore vasomotor tone, because its effects are very transitory. Its value as a stimulator of uterine contraction is undisputed.

### *Essential hypotension*

This is the name given to a syndrome whose chief objective finding is marked hypotension. Subjectively there is headache, vertigo and palpitation after even moderate exertion. There is marked fatigability, mental and physical. The cases cannot be classed under the psychoses. They occur most commonly in early adult life, more often in women than in men. Various theories have been advanced to explain the hypotension, none of which seem adequate. It is

admitted that there is a loss of vasomotor tone. To explain this, and the condition in general, a theory of capillary stasis due to histamin poisoning is submitted. Considerable evidence has been accumulated to justify such a view, though, admittedly, much work must be done before this hypothesis may be said to rest on the basis of established fact.

*Hypotension due to malfunction of the factors which normally maintain blood pressure*

*The cardiac factor* Temporary hypotension, due to the failure of the cardiac factor, is easy to understand, as, for instance, in typhoid fever. In chronic heart disease, however, failing circulation may be associated with a normal or even an increased blood pressure, owing to compensatory constriction of the peripheral arterioles. This peripheral vasoconstriction, however, necessarily reduces the capillary blood flow. The inability to increase the capillary flow during exercise is responsible for the muscular weakness and asthenia found with decompensated hearts. Furthermore, the hypertrophied heart is from the beginning a diseased heart, and with the advent and progress of more marked myocardial degeneration its reserve power is progressively reduced. During hypertrophy there is no proportionate increase in the heart's blood supply, so that the capabilities of the anatomically enlarged heart are, *ab initio*, somewhat restricted.

*Myocardial degeneration.* Hypotension is *not* common in the early stages of myocardial degeneration, though of course it occurs frequently in the terminal stages. What is more common is that, with a normal systolic pressure, the diastolic pressure rises. There is thus a marked diminution in pulse pressure. Speaking generally, it may be said that in myocardial disease, the smaller the pulse pressure, the lower the limit of cardiac reserve. Sudden drops in blood pressure in hypertensives are usually of serious prognostic omen, because they indicate rapid weakening of cardiac power. When, as part and parcel of myocardial degeneration, various arrhythmias occur, hypotension is rather frequently seen.

*Tachycardia* The hypotension usually seen in attacks of essential paroxysmal tachycardia is due to insufficient filling of the ventricles. The minute volume flow is reduced, the systolic pressure falls without

much change in the diastolic, so that pulse pressure is diminished. Where the attacks of paroxysmal tachycardia tend to increase in duration and frequency, the blood pressure level tends to sink permanently.

*Bradycardia* The drop in diastolic pressure is particularly marked in certain forms of bradycardia. Such pseudo-hypotension is probably due to the continued outflow of blood during the long diastole. In heart block, especially when associated with Stokes-Adams syndrome, hypotension is apt to be very marked, especially during the syncopal attacks.

*Premature contractions* It is believed that the existence of hypotension in association with premature contractions, other things being equal, is evidence of functional nature of the arrhythmia.

*Auricular fibrillation* Absolutely accurate estimations of systolic and diastolic pressures cannot be made during periods of fibrillation. "Average systolic pressure" may however be estimated. The rheumatic and arteriosclerotic groups show very different pictures, the pressures being naturally higher in the arteriosclerotic group. Average systolic pressures of over 110 mm in the rheumatic group, and of over 160 mm in the arteriosclerotic group, are of good omen. A falling average systolic pressure makes the outlook graver.

*Alternation* The outlook in persistent alternation is always grave. It is, however, increasingly threatening when marked hypotension accompanies it, because of the added evidence of myocardial degeneration.

*Valvular heart lesions* *Mitral lesions* The reestablishment of functional efficiency after a period of broken compensation in mitral lesions is often accompanied by a drop in arterial pressure.

*Aortic insufficiency* The association of high systolic and very low diastolic pressure affords presumptive evidence of the existence of aortic insufficiency. It is believed by some authorities that the systolic pressure is higher in arteriosclerotic aortic insufficiency than in the luetic type. This may be of aid in differential diagnosis as to type. A marked difference in arm and leg pressures in the recumbent type is very common in aortic insufficiency, and may be of diagnostic significance. The phenomenon is not limited to aortic insufficiency, however. An explanation recently offered is that the differential

pressure is due essentially to the transference of kinetic energy in a fluid in rapid motion, into stress, when the flow meets resistance

*Aortic aneurysm* The very low diastolic pressure, with increased pulse pressure, found in some cases of aneurysm without aortic insufficiency, may be accounted for by the forcing of blood into the reservoir of the aneurysmal dilatation during diastole

*The second factor The condition of the vessel walls*

Flaccid and toneless muscle fibres in blood vessel walls, due to the toxic influence of acute infection, may be a factor in acute hypotensions In arteriosclerosis hypotension is not uncommon Here the blood flows through the vessels as does fluid through unyielding tubes In such cases there is no periodic distention or contraction of the vessel lumen, and tension is therefore lowered

*The third factor Peripheral resistance determined by vasomotor tone*

It is believed by many observers that the peripheral resistance to the blood stream is the most important single factor in the regulation of blood pressure The endocrine system works in conjunction with the vasomotor system, exerting either a pressor or depressor action on vasomotor function It is now known that the capillaries play a very important part in the production and maintenance of vasomotor tone

*Syncope* Cerebral anemia results from an insufficient expulsion of blood from the heart Syncope may be due to vascular changes, relaxation of the arterioles, loss of tone in capillaries and veins. Sudden changes in the tone of the abdominal vessels are particularly apt to induce sudden hypotension, with its resultant symptoms

*Abnormal vasomotor tone* The theory of vagotonia and sympatheticonia rests upon the assumption that the balance between the parasympathetic and the sympathetic portions of the autonomic nervous system is upset An extensive literature has appeared on the subject, and some astonishing deductions have been based upon the theory The modern view is that the theory has not been proved

*Vascular crises* Most of the vascular crises are attended by marked rise of blood pressure Raynaud's disease is now being

treated by bilateral ramisection and ganglionectomy. The resulting vasodilatation produces relief of symptoms, with resulting drop in pressure. Changed vascular tone may lead to abnormal distribution of the blood mass. Thus if there be defective splanchnic innervation, there may be abdominal stasis with its resultant symptoms. But it must be admitted that a definite explanation of the mechanism by which the peripheral resistance becomes defective in cases of persistent hypotension is not perfectly understood. Testimony is accumulating to show that the agency which controls blood pressure through the peripheral resistance is the endocrine system. If this system is thrown out of balance, hypotension is apt to ensue and to remain persistent.

*The capillaries and blood pressure.* Capillaries possess powers of dilatation and constriction independently of the arterioles, and normally they maintain a state of constrictor tone. The factors entering into the mechanism of varying capillary constriction and dilatation are nervous and chemical stimulation. Nervous stimuli cause only constriction. Chemical stimuli may mediate both constriction and dilatation. The amount of blood which may, under circumstances be stored in the capillary bed instead of being returned to the general circulation is very large. There is extremely suggestive evidence that the capillaries are normally kept tonically contracted through the agency of the pituitary hormone.

There is still no agreement among investigators as to the actual pressure in the capillaries. It is obviously not permissible to speak of capillary pressure in the same sense as arterial pressure. Arterial pressure is a definite measurement, virtually the same in the large arteries throughout the body. Capillary pressures vary very widely in different parts of the body under normal physiological conditions.

The fundamental importance of the capillaries in the production of shock has already been discussed. A possible explanation of the low blood pressure in essential hypotension, based on capillary poisoning by histamin, has been mentioned. Capillary stasis is of prime importance in heart failure. The blood flow in the capillaries is a measure of the efficiency of the circulation.

The constitutional shock symptoms of burns, occurring before the period of infection, are due to material absorbed from the surface

An enormous capillary bed, potentially closed under normal conditions is opened up by a first or second degree burn. From the standpoint of therapy of burns, restriction of the rate of exchange and flow in the capillaries by the use of vasoconstrictor drugs, becomes a matter of importance. A new field in medicine is opening up, through the study of the activities, physiological and pathological, of the capillaries.

### *Hypotension in relation to endocrine disturbances*

*The adrenals* Despite much careful study, many phases of the physiology of the adrenals are still unsettled. The question of reflex or central control of the nervous mechanism is unanswered. It seems established that epinephrin causes stimulation of the heart, vasoconstriction in the splanchnic and cutaneous regions and dilatation in the skeletal muscle. But the so-called tonus theory, that arterial tone is maintained by the epinephrin constantly liberated, is not supported by physiologic evidence. The amount of epinephrin secreted spontaneously, would be, when diluted with the mass of blood of the entire circulation, quite inadequate to have any effect on blood pressure. There is still much discussion as to relative importance to life of adrenal cortex and medulla. The prevailing opinion may be tersely expressed in the summary of one physiologist: "The cortex is probably the indispensable part of the adrenal. The medulla apparently serves merely to reinforce the sympathetic system in times of stress."

A marked divergence of opinion between physiologic experimental study on the one hand, and clinical observation with reference to the adrenals, is manifest in the literature.

Certain physiologic studies on the relation of the adrenal to blood pressure are discussed.

*Adrenal insufficiency* It has not been possible to produce experimentally any well characterized symptoms associated with *partial* adrenal insufficiency. Clinically, cases of sudden death from adrenal insufficiency are reported. The physiological point of view is that proof must be adduced that the sudden death may properly be attributed to loss of adrenal function. The physiologists maintain that the adrenal medulla is not essential to life, while the preservation of

only a very small portion of the cortex may be compatible with apparent health and vigor. With reference to the hypotension, the physiologists point out that epinephrin is given off from the medulla and not from the cortex, that the maintenance of normal pressure does not depend to any important degree upon epinephrin. Hypotension is not caused even when the epinephrin output is totally suppressed. Fatal adrenal insufficiency is produced in animals by interference with the cortex.

There is thus no agreement, between physiologists and clinicians, as to adrenal insufficiency and the mechanism of its production. Clinically, three types of adrenal insufficiency are described, (a) the fulminating, rapidly fatal form, (b) the myasthenic form, (c) subacute or chronic forms, including Addison's disease. Tuberculosis may induce any one of these forms. Syphilis not infrequently attacks the adrenals. So also does the virus of certain of the acute infections. Adrenal insufficiency must not be diagnosticated on the presence of one or two symptoms, as found in Addison's disease. Another point of view stresses the fact that extreme adrenal insufficiency causes a clinical picture suggestive of acute poisoning. Chronic insufficiency is revealed by hypotension, skin bronzing and myasthenia. The muscle fatigability is marked, and in advancing cases is changed to muscle cramps, contractures and terminal convulsions. Clinical endocrinologists have ascribed all sorts of symptom complexes to adrenal insufficiency, without adducing particularly valid evidence to support their somewhat fantastic hypotheses. The clinical claims of results achieved by substitution organotherapy (usually whole adrenal substance) do not seem to rest upon the basis of carefully controlled study and critical analysis.

*The "white line" of Sergent.* There is increasing tendency in recent literature to deny the assumption that the white line of Sergent is a sign of adrenal insufficiency. Sergent himself now shares this view. Sergent's line is believed by many to be a vasomotor phenomenon indicating irritability of the vegetative system, not allied to any determined disorder. One investigator has studied the question carefully, including in his series the examination of 100 healthy subjects. The line was present in a large proportion of these persons. He considers it to be without pathologic significance.



*Adrenalectomy* In a discussion of the treatment of Addison's disease roentgen ray examination of the kidney region after oxygen insufflation into the bed of the kidney is advised. Where such examination shows only one adrenal to be tuberculous, its removal is indicated. Adrenalectomies have been done for other conditions also. The results have not been particularly encouraging.

*The pituitary* Certain types of dyspituitarism, notably hypopituitarism, are associated with hypotension. In some of these cases substitution therapy has been followed by good results.

*The gonads* Menopause hypertension is now a term in common clinical use. The assumption is that the internal secretion of the ovary has to do with the maintenance of blood pressure at or near normal levels. This influence is removed after the menopause and hypertension ensues. Clinically it is found that substitution therapy with ovarian extract is of value not only for the relief of the nervous symptoms of the menopause, but also for the relief of the hypertension. The ovarian secretion increases vagus tone and produces local vasoconstriction. On the other hand, the internal secretion of the testis produces changes of blood pressure only indirectly, by increasing the tone of the sympathetic system.

*Hypotension due to pluriglandular disturbances* It has long been believed that there are definite interglandular associations in the endocrine system. This hypothesis has been made the subject of experimental study, the preliminary report of which is available. It appears that the adrenals are positively and specifically correlated with all the other glands of internal secretion, save the hypophysis, in both sexes. The adrenals are an integrating agency, binding together the other incretory structures into an associative relationship. This influence is more general and more specific in the female than in the male. The solution of some of the problems of hypotension may be found in such relationships.

From the clinical point of view, there have been some exceedingly clear and reasonable statements of the achievements and the limitations of glandular therapy. These are discussed in some detail.

One author points out that asthenia (and hypotension) is common to many conditions of totally different origin. He says that the present tendency to blame the endocrine glands for every symptom is greatly to be regretted.

A summary of various classifications of hypotension is also presented

And finally it is pointed out that progress in the field of organotherapy will depend upon carefully planned, united efforts of physiologists, chemists, pharmacologists, pathologists, and clinicians

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*The Editors of MEDICINE wish to express their gratification that four men representing general medicine, pediatrics, and neurology, have consented to join the Editorial Board and share the considerable work of supervising the contents of the Journal. They are all of a training and standing especially suited to the work and all do it, in spite of heavy duties, as a service to the profession. Their names appear upon the cover.*



# REMEDIES RECENTLY INTRODUCED IN THE THERAPY OF AMOEBIASIS

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## INTRODUCTION

Investigations carried out during and since the World War have revealed a surprisingly high incidence of amoebic infection in man not only in tropical but also in temperate zones. An increasing number of publications report cases of this disease, which was formerly considered tropical, in persons who have never left the temperate zone and its higher standard of sanitation.

Table 1, from J. G. Thomson's article (75), gives a synopsis of the surveys made in recent years of infestation with protozoa of population groups almost all over the globe. To understand why this knowledge was not obtained earlier we have only to realize what a stupendous amount of highly specialized work is summarized in this table. One has to keep in mind that according to most of the experts

1 Six stool examinations are necessary to rule out the presence of *Entamoeba dysenteriae* in the feces, and this with only about 90 per cent probability.

2 Five, and, by some authorities, six, species of entamoeba are found in human feces, namely, (a) *Entamoeba dysenteriae* (*histolytica*), (b) *Entamoeba coli*, (c) *Endolima nana*, (d) *Jodamoeba butschlii*, (e) *Dientamoeba fragilis* (Jepps), (f) and, finally, the disputed species, *Councilmania Lafleur*. In addition, one has to consider that *Entamoeba gingivalis* may appear in the feces.

3 The differential diagnosis, which is based on morphological characteristics, has to be done by an expert, the final diagnosis is usually done with a permanent (iron haemotoxylin) stain and the necessary search of about ten smears cannot be done in less than three hours time.

TABLE 1  
Table of surveys of human faeces for intestinal protozoal parasites

(Human Entamoebiasis in Temperate Zones, by J G Thomson Journal of State Medicine, 33, 1925 P 568-73 )

OBSERVER	LOCALITY	TYPES OF INDIVIDUALS EXAMINED	NUM- BER OF CASES	NUMBER OF EXAMINA- TIONS PER CASE	PERCENTAGES OF POSITIVE FINDINGS						
					E his- tolytica	E coli	E nana	I butsi- chli	Giardia	Chlo- mastix	Tricho- monas
Matthews and Smith, 1919	Liverpool, England	Recruits in camp England	1,098	1	5.6	18.2	5.5	0.4	7.0	0.18	0
Idem, 1919	Liverpool, England	Adult civilians, Royal Infirmary Never out of England	450	1	1.5	6.7	2.4	0	6.0	23.0	0
Idem, 1919	Liverpool, England	Children under 12 England	548	1	1.8	11.1	2.7	0.18	14.1	1.8	0
Idem, 1919	Liverpool, England	Asylum cases (Whittingham)	207	1	9.7	45.9	12.1	0	3.4	23.2	0
Idem, 1919	Liverpool, England	School cadets	41	1	2.4	26.8	2.4	0	2.4	0	0
Smith, 1919	Liverpool, England	Asylum cases (Ranhill)	504	1	4.2	21.4	3.0	0	5.0	6.7	0
Dobell, 1921	England	Civilians never out of England, Army recruits, hospital patients, etc., excluding asylum cases	3,146	Mostly sun- gle et- amina- tions	3.4	18.1	4.6	0.25	9.3	2.9	0
work of Matthews and Smith, also of records by Goodey, Thacker, Camp- bell, Nutt and McLean	Leeds, Birmingham										
Bach, 1924	Germany Rhine, Province	Inhabitants, adults, 214, children (under 15), 221	435	1	6.0*	23.2	7.8	4.8	14.9	1.4	0
Kofoid and Swezy, 1920	United States	Overseas troops	2,300	1+	12.8	20.5	29.3	0	5.7	4.2	0.1
Idem, 1920	United States	Home Service troops	576	1+	4.3	15.9	27.8	0	6.4	3.5	0.5
Kessel and Svensson, 1924	China Peking	Foreigners, all ages	221	1	10.0	12.8	15.8	1.3	13.0	3.6	0.8
Idem, 1924	China Peking	Chinese, all ages	816	1	14.1	17.6	22.4	4.6	4.9	1.3	0.7
Maplestone, 1921	Queensland	All ages	500	1	4.6	26.4	0	0	11.8	2.2	0
Young, 1922	Amazonas, Brazil	School children	249	1	22.5	36.9	0	0	14.0	2.8	0
Maplestone, 1924	Sierra Leone	Native men in gaol	500	1	15.0	43.6	9.8	13.0	2.2	1.8	2.2
Wenyon, 1916	London	Convalescent soldiers	556	1	10.8	39.0	1.0	5.2	16.0	0.7	1.6
Wenyon and O'Connor, 1917	Egypt Alexandria	Convalescent soldiers	328	Mostly 1	6.4	31.7	0	2.0	5.4	0.9	0.6
Idem, 1917	Egypt	Hospital cases	961	Mostly 1	3.2	10.4	3.0	0.3	6.0	2.8	3.0
Idem, 1917	Egypt Garbari Prison	British prisoner	168	Mostly 1	1.8	12.0	12.0	0	6.0	3.2	2.4
Idem, 1917	Hadra Prison	Healthy native prisoners	524	Mostly 1	13.7	48.6	0	14.8	0.57	0.19	0
Idem, 1917	Egypt	Native cooks	87	Mostly 1	11.5	20.7	0	7.0	7.0	1.1	1.1
Idem, 1917	Egypt	Healthy British troops	1,979	Mostly 1	5.3	20.0	0.5	3.0	4.8	1.1	1.1
Idem, 1917	Egypt	B W I cooks	48	Mostly 1	4.1	18.7	0	4.1	4.1	0	0

	England	Liverpool	Healthy young men in camp	Soldiers	206	1	3 9	10 7	0	0	4 3	0	0
Yorker Carter Mackinnon Mathews and Smith 1917	England	Liverpool	Surgical cases	Royal Infirmary	138	1	1 4	2 8	0	0	3 6	1 4	0
Idem 1917	England	Liverpool	Home Service troops		2 584	1	3 5	20 3	12 5	6 0	6 0	3 1	0
Berk and Stiles 1923	United States		Foreign Service troops		3 536	1	2 8	13 1	11 9	4 1	5 5	1 5	0
Idem 1923	England		Healthy recruits to Royal Navy		400	1	2 5						
Baylis 1919	England		Dysentery patients in hospital		3 277	2 to 4	15 4	19 5	2 6	2 3	10 4	2 7	1 or 2 cases
Turner and Taylor													
Dobell 1917	Britain		Returned troops		2 000	3	12 6	40 5	0	0	16 1	0	0
Brug 1920	Java		Natives		150	3	23 0	0	0	8 0	0	0	0
Idem 1920	Java		Europeans		100	3	27 8	0	0	12 0	0	0	0
Faust and Vassell 1921	China	Wuchang	Chinese		143	Average 3	24 5	16 8	4 2	0	3 8	0	10 7
Jepps 1923	Malay		Natives and Chinese		1 034	3	14 5	7 7	2 2	0 4	4 2	2 5	11 5
Kessel and Svensson 1924	China	Peking	Foreigners all ages		105	3	13 4	25 6	20 8	2 8	2 8	5 6	0 9
Idem 1924	China	Peking	Chinese all ages		368	3	20 7	23 6	32 0	7 3	8 0	4 3	2 1
Smith and Matthews 1917	England		Non-dysenterics returned from abroad		200	About 3 per case	7 5	23 5	0	0	11 5	2 0	0
Jepps, 1921	England		Dysentery cases, etc		971	1 to 6	23 7	30 4	28 6	3 1	13 2	6 5	1 2
Mackinnon 1918	England		Dysenterics and non-dysenteric cases		1 680	1 to 6	12 4	26 2	18 0	0 7	13 4	5 0	0 7
Smith and Matthews 1917	England		Non-dysenteric soldier patients		250	1 to 6	8 0	19 2	0	0	8 0	2 0	1 7
Carter Mackinnon Mathews Smith and Stephens 1917	England		Soldiers in hospitals and camps		1 713	Average 5 2	10 9	29 4	0	0	18 5	3 5	1 0
Kofoid and Szezy 1920	United States		Dysenteric convalescents		53	6	26 5	29 0	64 0	0	2 9	5 8	2 0
Dobell 1921 (vide supra)	England		Home Service troops		3 146	Corrected to 6	7 0-10 0	36 5	9 0-13 0	0 5	18 0-2, 0	6 0-9 0	0
Kessel and Srenson 1924	China	Peking	Civilians never out of England		151	Corrected to 6	25 0	33 5	32 0	4 5	2 5	14 0	4 5
Idem 1924	China	Peking	Foreign adults		221	Corrected to 6	16 5	26 1	26 5	3 2	3 0	1 0	2 8
Idem 1924	China	Peking	Foreigners all ages		200	6	32 5	29 5	38 5	15 5	6 5	6 5	4 5
Idem 1924	China	Peking	Chinese adults		275	6	29 5	30 9	40 1	13 0	10 0	6 0	4 5
Faust, 19 4	China	Peking	Chinese all ages		60	1 409 examina- tions	20 0	0	45 0 per cent had protozoal infections				
			Patients in medical ward										
Le Nor and Deschiens 1924	Paris		Adult males mostly Colonial patients suffering from gastric or colon troubles		1 000	1	5 0	30 5	0 5	0	7 5	0 2	0 3

\* Adults 3 9 children, 2 1



~~The~~ ~~white~~ ~~and~~ ~~hepatitis~~ were formerly commonly known as ~~manifestations~~ of amoebiasis, many experienced physicians now con-  
~~sider~~ ~~that~~ ~~amoebiasis~~ may cause a considerable variety of symptoms,  
~~not only~~ of gastro-intestinal but also of general character, in periods  
of varying length with different intervals. The eradication of the  
~~amoeba~~ is considered a most difficult task. While the motile forms or  
~~trichomonites~~ are comparatively easily destroyed, the cysts show a  
considerable resistance to most therapeutic agents.

There is by no means unanimity regarding the significance of the  
appearance of the cysts in the feces. That *Entamoeba dysenteriae* is a  
true tissue parasite living in ulcers of the intestinal tract is accepted  
fairly generally. Dobe's theory that an equilibrium ordinarily exists  
in the relation between host and parasite is considered very plausible.  
The hypothesis that clinical manifestations appear only when this  
equilibrium is disturbed, for instance by a diseased state of the para-  
site or by other unknown factors, is adopted by many authors as  
explanation of the fact that only a small percentage of people excreting  
cysts ever show clinical symptoms. This view is supported by Yorke  
and A. J. S. (86) who state that "the presence of the cyst and  
encysted forms in the feces is not sufficient to establish the diagnosis  
of amoebiasis."  
The fact that the cysts are not pathogenic in the experimental  
animal is also in favor of the view that the cysts are not pathogenic.  
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men have not been repeated on a large scale since Walker and Sellards (81) experimented on 20 volunteers, 18 of whom became infected. A very promising precipitation test worked out on cats by Wagener (80) has so far not proved of value in man. Thus the laboratory diagnosis seems to have reached the limit of its usefulness and practicability in differentiating the species of amoeba in man and determining their pathogenicity and virulence. The culture method established by Boeckh and Drbohlav (7) is now the hope of protozoologists in their efforts to make further progress.

Clinical methods of investigation have aimed chiefly at obtaining material more directly from the site of habitation of the amoeba, such as duodenal drainage and proctoscopy or sigmoidoscopy, the latter of which often permits diagnosis from the appearance of the mucous membrane. Provocative drugs, saline laxatives, bile, emetine and yatren, often give positive results when spontaneous movements are free from cysts.<sup>1</sup> X-ray of the colon is said to demonstrate filling defects characteristic of amoebic ulcers (Vallarino (76)).

#### EMETINE AND SOME OTHER EARLIER THERAPEUTIC MEASURES

Emetine, introduced by Rogers (67) and Vedder (78), has been the sovereign remedy for amoebic colitis and hepatitis since 1912. Its action on the acute manifestations is as prompt as that of any specific remedy. Amoebic liver abscess, formerly frequent and the most common cause of death, has become rare since its introduction. But eradication of *Entamoeba dysenteriae* is rarely obtained by the doses commonly used. Combination of emetine hydrochloride subcutaneously or intramuscularly with emetine bismuth iodide or emetine periodide and emetol (an emetine base in ether oil) (Willmore (84)) *per rectum* has been employed to eradicate the amoeba from the tissues. Even with ever increasing doses, however, the percentage of permanent cures is low, varying according to different reports under tests of varying severity from 28 to 70 per cent. The dissatisfaction of physicians with this drug is illustrated by the steady increase of the

<sup>1</sup> Provocative measures, especially the administration of bile, are irritating and only permissible if the patient's condition and the circumstances do not prohibit their being followed by satisfactory treatment.

TABLE 2

*Acute, sub-acute, and chronic cases of amoebiasis indigenous in Europe*

From Thomson, J. G. Human Entamoebiasis in Temperate Zones Journal of State Medicine

OBSERVER	YEAR	COUNTRY	PLACE OF OBSERVATION	DETAILS OF CASES
Dickinson	1862	England	St George's Hospital, London	Post-mortem on a woman Intestinal ulcers Abscess of liver
Dickinson	1881	England	St George's Hospital, London	Post-mortem on man Ulcers of large intestine Abscess of liver
Moore	1881	England	St Bart's Hospital, London	Post-mortem on girl, aged 3½ Ulceration of large intestine Two abscesses of liver
Saundby and Miller	1909	England	Birmingham	Amoebic dysentery with abscess of liver Amoebae found in intestine and liver
Marshall	1912	Scotland	Edinburgh Royal Infirmary	Amoebic dysentery in ploughman Cured by emetine
Woster-Drought and Rosewarne	1916	England	Royal Herbert Hospital	Acute amoebic dysentery <i>E histolytica</i> found Cured by emetine
Laidlaw	1917	England	Guy's Hospital	Three cases (1) Chronic amoebic dysentery (2) amoebic abscess of liver Cysts of <i>E histolytica</i> in faeces (3) Dr Perdrau's case Tissue of large intestine and liver abscess <i>E histolytica</i> found
Malins Smith	1919	England	Asylum, Liverpool	Out of 60 cases of acute dysentery 3 were amoebic, i.e., 5 per cent
Young	1921	England	Paddington Green Hospital	Child, aged 3 years Numerous <i>E histolytica</i> found
Galliard and Brumpton	1912	France	Paris	Acute amoebic dysentery Male, age 25 <i>E histolytica</i> found
Paviot and Garni	1913	France	Lyons	Fatal case of amoebic dysentery

Landouzy and Debré	1914	France	France	Fatal case, amoebic abscess of liver
Ravaut and Krolunitski	1916	France	France	25 cases of acute amoebic dysentery
Neveu Lemaire and Zembouls	1919	France	France	Amoebic dysentery and malaria
Labbé	1919	France	Paris	Eight cases of amoebic dysentery
Gann and Lepune	1924	France	Lyons	Forty cases of amoebic dysentery
Kuenen	1918	Holland	Holland	abscess cases (1) Boy, aged 12 Intermittent dysentery <i>E. histolytica</i> (free forms) found (2) Boy, aged 12 Precystic and cystic <i>E. histolytica</i> Later blood and mucus (3) Woman, aged 32 Diarrhoeic attacks Occasional blood and mucus since 18 years of age (4) Daughter of above case (3) Blood and mucus <i>E. histolytica</i> cysts found (5) Woman, aged 32 Fourteen years' intermittent diarrhoea Cysts found Man, aged 25 Colitis with blood and mucus <i>E. histolytica</i> found Man, aged 25 Colitis with blood and mucus <i>E. histolytica</i> (free forms) found (1) Girl, aged 18 Diarrhoea for 18 months <i>E. histolytica</i> (free forms) found (2) Young soldier with dysentery Cysts and active amoebae found Man, aged 36 Diarrhoea Blood and mucus <i>E. histolytica</i> found Post mortem Amoebic ulcers of caecum and abscess of liver
Ennelling	1921	Holland	Holland	
Van der Hoeven	1921	Holland	Holland	
Fischer	1920	Germany	Germany	
Jones	1921	New Zealand	New Zealand	
Cleland	1923	Australia	Australia	

doses of emetine used. In 1917 Wenyon and O'Connor (83) considered the administration of 12 grains subcutaneously and 6 grains by mouth, over a period of twelve days, efficient. In 1923 Willmore and Martindale (85) found a twenty-day treatment with 10 grains of emetine hydrochloride subcutaneously and 60 grains of emetine bismuth iodide by mouth efficient in only 28 per cent of their resistant cases.

The efficient dose of emetine is so near the toxic dose that toxic doses are almost always given. The symptoms of emetine poisoning, usually ascribed to polyneuritis resembling alcoholic or arsenical neuritis are very common in a slight degree during the course of ordinary treatment, and even a few deaths have been ascribed to its action. A recent publication by Young and Tudhope (87) gives the following conclusions regarding the toxic action of emetine.

1. Emetine is a protoplasmic poison, acting equally on all tissues, heart failure being the actual cause of death
2. In cases where the heart or kidney is affected it is advisable to give as small a dose as possible
3. In an otherwise healthy individual it would appear advisable to limit the number of doses as far as possible and not to give, within twenty-four hours, more than 1 grain of the drug
4. The weakness produced after emetine administration is probably the result of the direct action of emetine on the muscle protoplasm
5. Neuritis (of the alcoholic or arsenical type) is not produced by emetine, but degeneration of the motor fibres (as in lead palsy) may occur

The discomfort and danger caused especially by the prolonged administration of emetine form a serious obstacle to its use in cases of cachexia and of diseases of the circulatory organs. The prolonged invalidism following the customary course of treatment makes its use appear unreasonable in cases showing little or no impairment of general health and working ability. The economic loss connected with it seems so great that any less toxic drug would be welcome.

For intestinal amoebiasis many experienced physicians (James and Deecks (35), Willmore and Martindale (85)) have used bismuth subnitrate in large doses (one teaspoonful several times a day) combined with emetine. Ziemann (89) commends bismuth subnitrate with Karlsbad salts.

Native plants belonging chiefly to the *Simarubaceae* have supplied drugs enjoying considerable reputation locally. Chaparro amargosa (*Castela nicholsoni*) is the only such drug, according to references available, which has been studied systematically (Sellards and McIvor (72) and French and Sellards (25)). None of them have been tried in a sufficiently large number of satisfactorily followed cases to permit the formation of a definite opinion regarding their efficiency.

Van der Togt (77) has used 40 per cent sugar solution as enema for the purpose of changing the osmotic pressure in the intestines, with apparently good clinical results.

de Rivas (65) and Andresen (1) use duodenal or colonic irrigation of hot water (42° to 47°C) in combination with magnesium sulphate.

That a special diet may favor spontaneous clearances from entozoa has been demonstrated on rats by Hegner (30) (meat diet). Kessel and Huang (38) used milk diet with monkeys and children. The experience of the latter conforms with the empirical knowledge which holds milk diet in high esteem in the treatment of chronic colitis and points to wider possibilities of dietetic treatment.

All attempts to remove amoebae only from their common site of habitation, important as that is, seem insufficient or futile in the light of the modern conception which tends to consider amoebiasis as a systemic infection similar to syphilis.

#### YATREN

Three types of drug have appeared during recent years as anti-amoebic remedies which have been tried systemically, namely, yatren, the arsenicals, stovarsol and treparsol, and the coal tar derivative, auramine.

Yatren is a product of the German chemical industry, in use since 1912 under many different names, tryen, griserinneu, loretin, xantropin, xantren, as a non irritating antiseptic for use in surgery instead of iodoform. Mühlens (57, 58) introduced it into the treatment of amoebiasis. Yatren purissimum 105 is produced by the Behring Werke, Marburg. The chemical composition as given to Mühlens is

Iodine	5 parts	} containing 28 per cent of iodine
Oxy chinoline	8 parts	
Sodium sulphonate	7 parts	

doses of emetine used. In 1917 Wenyon and O'Connor (83) considered the administration of 12 grains subcutaneously and 6 grains by mouth, over a period of twelve days, efficient. In 1923 Willmore and Martindale (85) found a twenty-day treatment with 10 grains of emetine hydrochloride subcutaneously and 60 grains of emetine bismuth iodide by mouth efficient in only 28 per cent of their resistant cases

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Iodine	5 parts	} containing 28 per cent of iodine
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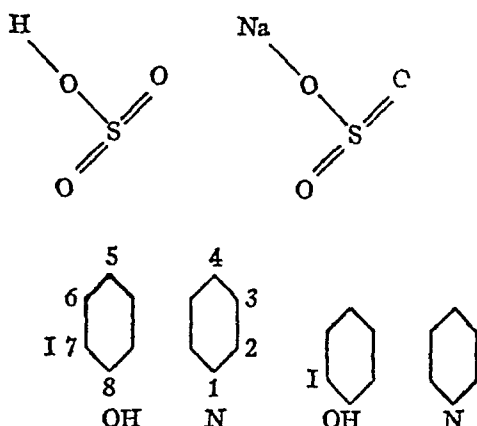


Sodium bicarbonate, 20 per cent, is added to increase its solubility it is a yellow, tasteless powder, light and easily dissolved in warm water up to 5 per cent. It does not disintegrate with heat until a temperature of 223°C. is reached and then becomes toxic because iodine is split off.

Kop (44) constructs the following formula for yatren:

8 oxy, 7 iodine chinolin, 5 sulfo-acid, with 20 per cent sodium bicarbonate

In solution this is:



### Laboratory investigation

Herzberg (31) found no consistent results in testing the bactericidal power of yatren. Combination with proteins seems to increase its potency, as also occurs in the case of arsphenamin. In low concentration there is flocculation of the protein solutions, which dissolves after the addition of more yatren. This flocculation is strongly influenced by the reaction of the solution.

Breitenstein (9) found yatren *in vitro* especially bactericidal for streptococci, which were killed in 12 hours in a dilution of 1:10,000. Less marked effects were observed on the typhosus group *Bacillus dysenteriae* of Shiga and *Bacillus abortus* were killed in a dilution of 1:400 in six hours. Yorke and Adams (86) found yatren in 5 per cent solution not active against *Entamoeba dysenteriae* in culture after thirty minutes at 37°C. Kofoed and Wagener (43) found that it killed *Entamoeba dysenteriae in vitro* in a dilution of 1:1250 in twenty-four hours. The toxicity of pure yatren for mammals is very slight.

Rabbits, horses, and cattle tolerate enormous doses, mice of 15 grams weight are killed only by 0.5 cc. of a 5 per cent solution subcutaneously (Breitenstein (9)). Schubel (70) found the lethal dose for mice and rats to be 0.6 gram, for cats 0.36 gram, per kilogram body weight. Herzberg (31) considers the saturation of the sulpho compound in the benzol ring the probable cause of its non-toxicity.

Dietrich (17) observed neither hemolysis nor interference with the action of leucocytes in the presence of yatren. The latter observation was confirmed by Yamaguchi, who, according to Hata (29), reports favorable action of yatren on phagocytosis.

Kessler (40) showed that by examining the urine after yatren application iodine is split off in the body. He found after injection no excretion of the drug in the urine. Yatren as demonstrated by the ferric chloride method<sup>2</sup> is present after parenteral administration in the urine for only five and one-half to ten hours, but iodine is excreted for five or six days. Iodine elimination lasts longer after intravenous than after intramuscular injection. Herzberg (31) however found in two cases yatren quantitatively eliminated five and one-half to six hours after intravenous injection. After oral administration Kessler found a delayed, diminished and shortened period of elimination of yatren, and delayed and diminished excretion of iodine. This he attributes to increased excretion through the intestine. Schubel (70) considers the question of elimination of yatren by no means settled.

As stated above, yatren disintegrates at 223°C and is then toxic and irritating. Boiling for fifteen minutes has practically the same effect. The probable chemical change is considered to be the liberation of hydrogen iodide, which gives rise to free iodine.

Regarding the mechanism of its action, yatren is thought to belong to the group of bodies acting through cell stimulation or, as Weichardt (82) puts it, omniscellular activation of protoplasm.<sup>3</sup> The direct amoebicidal potency of yatren *in vitro* is low. Ruge (69) thinks the bactericidal qualities may partly account for the effect. Ziemann

<sup>2</sup> The presence of yatren in the urine may be shown by the addition of a few drops of ferric chloride, when a green precipitate appears. This is a simple and useful control.

<sup>3</sup> Cf. Jochmann, Erich. Histo-haemorenale Verteilungsstudien Yatren. Zeitschr. f. Klin. Medizin, 1926, v. 104, 255-293.

(89), apparently considering the sodium sulphonate part of yatren its potent factor, is trying to replace yatren by Karlsbad salts, adding bismuth subnitrate as the protozoocidal agent

### *Administration*

Yatren was first used as enema with spectacular benefit in severe chronic cases which had previously resisted any form of treatment. The 5 per cent solution used in the first cases was later found not to be well tolerated by most patients, and the 10 per cent solution, employed by a few authors (Birt (6), Reiss (64)) has caused considerable irritation. Recent workers have gradually diminished the concentration to 2.5, 1.5 and 1 per cent. Huppenbauer (32) and Muhlen (57, 58) found that concentrations of 2.5 per cent, which are irritating for some patients, are easily tolerated in high colonic irrigations. Most observers, including the present writer, have found 1.5 per cent satisfactory, that is, 3 grams in 200 cc of distilled water. Huppenbauer introduced Brosch's enterocleaner and uses 1 to 3 grams of yatren in 10 to 20 litres of distilled water for colonic lavage.

By mouth, yatren has usually been given in wafers or gelatine capsules of 0.5 gram four to six times a day, or in pills of 0.25 gram, four pills, three times a day. Yatren by mouth usually causes diarrhea, with three to six soft or semi-liquid stools of light yellow colour. This diarrhea usually subsides twelve to twenty-four hours after discontinuation of the drug. Enemas have a less laxative action, but as daily enemas prove too irritating for many patients, alternate treatment per os and per rectum has been instituted by several workers and, in the author's experience, this method has been practical. The ordinary dose of 3 grams per day is sometimes too large, and patients have been seen who seemed to be hypersensitive to the drug, as Muhlen (57, 58) reports. He mentions one patient with whom he had to begin at 0.05 gram a day, gradually increasing this dose to 1 gram and extending the treatment over several weeks.

In this hospital for two years we have been using the following routine. First, third, fifth, seventh day, yatren 0.5 gram by mouth six times a day. Second, fourth, sixth, tenth, fourteenth, twenty-first day, an enema containing 3 grams of yatren in 200 cc of distilled

water, after a cleansing enema which is retained for several hours. This we call one course of yatren. It is repeated if indication arises. Several courses of five to ten days duration, with a daily dose of 3 grams, have been advocated by most authors (Muhlens (57, 58), Menk (55), Manson-Bahr (50, 51), and others). The chief precaution seems to be to avoid desiccation and discomfort. Any increase of the diarrhea or colic is an indication to interrupt the treatment for a day and to try smaller doses if the symptoms recur. Katsurada (37) uses 0.6 gram, Bejnen (4) 0.5 to 0.75 gram, three times a day, with good results. Enemas in lower concentration, namely, 1 per cent, have been used efficiently. Ruge (69), however, states that doses below 3 grams a day are not reliably efficient.

Many patients tolerate this as an ambulatory treatment without special diet (Menk (55) and de Langen (46)), but individual treatment is giving the best results, and hospitalization during the first seven days is often advisable. Adjustment of dosage, diet and complete rest are so essential that Manson-Bahr (50, 51) and the writer prefer it to ambulatory treatment. Our observations show that of 88 patients treated, 9 had relapses and 7 of these were receiving ambulatory treatment.

For children, solutions of yatren have been used in doses roughly proportionate to their body weight. Buchmann (12) reports that it is well tolerated and effective.

### *Results*

The most spectacular effects were obtained in old chronic cases which had previously resisted all forms of treatment (Huppenbauer (32), Muhlens (57, 58), Menk (55), Olpp (60), Kuenen (45), Mello Silva (53), Kop (44), de Langen (46), Laube (47), Bax (3), Manson-Bahr (50, 51), Bach and Steinbauer (2)). In cases of amoebic colitis the immediate effect of yatren is usually a rapid improvement in general condition and in the quality of the stools. Amoebae, with rare exceptions, disappear not later than the third day of treatment and at the same time the number of other protozoa is usually markedly diminished. Flagellates seem to be less influenced than by the arsenical preparations (see below). Most patients volunteer the

statement that they are feeling better, but in many cases there is no effect at all on the subjective condition

Regarding the final results, we must consider, as in the case of all the other drugs, that the same standard has not been applied by the different observers in following the patients and the word "cure" is always used very reluctantly. Kressel and Willner (39) consider freedom from clinical symptoms of dysentery and six negative stool examinations by the same method by which infection was discovered, three to six months after treatment, as the test of the efficiency of the treatment. In the Peking Union Medical College Hospital out of 88 patients followed for a period of from three to six months, with three to six stool examinations, 79 remained free from symptoms and cysts.

Muhlens (57, 58), using provocative measures (saline laxatives, bile), and sigmoidoscopic examination, reported at the last Congress of Tropical Medicine 30 per cent relapses, most of them without clinical symptoms. In his review, "Five years of yatren treatment," he states that the percentages of "cure" reported by different authors range between 66 and 92.

In acute amoebic colitis the effect of emetine is so striking that neither Muhlens (57, 58) nor the majority of other authors wish to abandon it, although many workers give favorable reports from the exclusive use of yatren and some, Rodenwaldt (66), for instance, consider emetine unnecessary. But van Steenis reports a good many cases of troublesome diarrhea following yatren by mouth, and enemas are also apt to be irritant during the first days. Three to six intramuscular injections of 0.065 gram of emetine are usually given on the first few days of yatren treatment. A combination of yatren and emetine, issued under the name of emetren, for injection, does not seem to have any advantage.

Yatren alone and in combination with emetine and conservative surgical procedures has also been successfully used in a few cases of liver abscess.

#### *Other uses of yatren*

It is not surprising that occasional cases of sprue have been benefited by yatren, for amoebiasis is not rarely disguised under this clinical picture.

Laboratory evidence (Breitenstein (9) and others) has encouraged the use of yatren in bacillary dysentery. It is reported to be efficient, thus recommending itself for use in cases of mixed or doubtful origin. There is, however, no evidence that yatren is more effective for this purpose than the cheaper saline laxatives in proper doses. Its indiscriminate use may lead to negligence in making a proper diagnosis and many cases of amoebiasis might thus escape proper later study and periodic treatment. It would be as faulty as purely symptomatic treatment of malaria or syphilis. Yatren has been used in other diseases, as *Schwellenreiztherapie* in Germany, quite extensively without any untoward effect, either singly or combined with casein or bacterial vaccine. Sera preserved with yatren show no toxic effects. Regarding other uses of yatren see Duehrssen (18).

In veterinary medicine it has been used subcutaneously with benefit in actinomycosis of cattle and in lymphangitis epizootica (Pfeiler and Oberlaender<sup>4</sup>). Eckert (19) reports one case of oral actinomycosis in a man cured by large quantities of yatren intravenously.

### Discussion

Unsatisfactory results of the use of yatren were seen by Gordon (27), one incompletely treated case, Lichtenstein (49), who changed his opinion later, and Birt (6), who used too high a concentration of the drug. Boyers, Kofoid and Swezy (8) state that they never saw a clearance from amoeba by yatren alone and consider it as a mere adjuvant. Willmore and Martindale (85) found it entirely inefficient, not even relieving the clinical symptoms in four refractory cases of chronic amoebiasis. They think, however, that yatren ought to have been tried through appendicostomy. No statement is made as to whether these cases yielded to any other kind of treatment. Castex (14) mentions one case treated with yatren for eight months without results. In spite of these failures, yatren, as indicated above, has been sufficiently successful to merit continued trial. There are no reports of toxic effects by enteral administration, the only danger lies in desiccation as the consequence of profuse watery diarrhea, and this is usually well controlled by discontinuation of the drug and

<sup>4</sup> Cited by Breitenstein (9)

administration of glucose or Ringer's solution parenterally. Albuminuria is mentioned by Ruge (69) and Evler (21) as a possible sequel, but this is ascribed by others to concurrent infections. In this hospital we have had one death following yatren treatment. The patient was a man of sixty-five suffering from joint tuberculosis with severe acute amoebic colitis and marked malnutrition, to whom were given by mistake massive doses of sodium sulphate in addition to yatren. Later he received a few doses of emetine. His course was persistently unfavorable in spite of the administration of glucose and saline solutions intravenously. Autopsy was not obtained, but the death can hardly be attributed to yatren.

Toxic effects were observed by Zieler and Birnbaum (88), who used yatren intravenously in the treatment of gonorrhoea and syphilis, with two deaths from acute yellow atrophy of the liver. The solution had been sterilized before administration, which must have caused the liberation of iodine. For amoebiasis only oral and rectal administrations are indicated (Muhlens (57, 58), Menk (55), Olpp (60), Huppenbauer (32), and Kuenen (45)).

The hesitation to use yatren is partly due to its being a proprietary drug and to its price, which is prohibitive in many countries, especially in the United States. Kessel and Willner (39) found it less expensive than emetine treatment for healthy carriers. Shiga, at the 18th Biennial Conference of the China Medical Association, mentioned that the Sankyo Company of Tokyo is issuing, under the name of "pyri-form," a drug similar to yatren prepared under Hata's direction. This preparation is said to have given satisfactory results in Japan, Korea and Formosa.

#### ARSENICAL PREPARATIONS

Arsenical preparations have been in use for the treatment of amoebiasis since 1915. American surgeons were among the first to report the clinical cure of amoebiasis in luetic patients following arsphenamine treatment. Arsphenamine and neoarsphenamine were given intravenously in the course of emetine treatment. Milian and later Ravaut (63) first used the arsenobenzenes by mouth in the form of gluten-covered tablets of novarsenobenzol, 0.1 gram once or twice daily. Later Ravaut found arsenobenzol by mouth most satisfactory, stable,

efficient and well tolerated in a dose of 0.2 to 1 gram for several days. There was clinical improvement and cysts of *Entamoeba dysenteriae* disappeared in two days and cysts of *Lambia* in five days. Ravaut advises beginning the treatment of chronic cases with 0.5 to 0.6 gram of arsphenamine daily, diminishing this amount rapidly to 0.2 to 0.3 gram a day and maintaining this dose for several days, with or without ipeca-cuanha-bismuth paste at the same time. For acute and subacute cases he recommends intravenous treatment. As preventive doses 0.1 to 0.3 gram by mouth twice a week may be given. There is no report of intoxication. Gunn (28), Kofoid, Boyers and Swezy (42), Brown (10), and Lichtenstein (49) have used arsphenamine in combination with emetine and report favorable results.

The trivalent arsenobenzenes have, however, not been used alone in the treatment of amoebiasis upon a sufficiently large scale to justify definite conclusions as to their efficacy.

More extensive experience is available with two pentavalent arsenical compounds introduced into therapeutics in 1922 under the names of stovarsol and treparsol.

Acetyl-amino-phenyl-arsinic acid, which is one of these compounds, was first prepared in Germany by Ehrlich, Benda and Bertheim (20) as No. 495 of their series, but it was not examined systematically by these authors as Ehrlich had centered his interest on the trivalent arsenobenzenes. Fournieu and the Trefouels (24) reprepared almost all the members of this group and tested two especially amino-oxy-phenyl-arsinic acid (No. 189), which they called treparsol, and acetyl-amino phenyl-arsinic acid (No. 190) or stovarsol.<sup>5</sup> Levaditi (48) and Navarro-Martin (24) found stovarsol efficient as an anti-syphilitic by oral rather than by parenteral administration, first for prophylactic, later also for curative, purposes. Jacobs (34) in an earlier issue of this review, discussing the value of the trivalent and pentavalent arsenicals, makes a statement about tryparsamide which is peculiarly fitting to the present subject.

Since the biological activity was an exhibition of a property of some form of trivalent arsenic, it was undoubtedly a logical step, if considered alone,

<sup>5</sup> The name of the identical German preparation is spirocid, that of the Russian stovarsolan.



Emetine in addition apparently did not change the effect greatly. Two mild arsenical rashes were observed. The authors think the proper dose has not yet been determined.

Smaller numbers of cases were reported by Bernard and Thomas (5), Cade and Ravaut (13), Delanoe (16), Spencer (73), Rubenthaler and Jansion (68), Nogue and Leger (59), Manson-Bahr (50, 51), and Couvy (15).

Petzetakis (62) used stovarsol combined with emetine in a large number of cases. He recommends the following doses for children:

	<i>grams</i>
1 year . . . .	0.05-0.08
2 years . . . .	0.08-0.1
3 years . . . .	0.1-0.15
5 years . . . .	0.15-0.25

Petzetakis does not believe that stovarsol has a quick action and finds relapses frequent. He recommends it chiefly as a prophylactic.

Kofoed (8, 41, 42, 43) and his co-workers and Brown (10) consider stovarsol useful only as an adjuvant.

Garin and Lepine (26) recommend the following routines for stovarsol administration.

- a.* A course of four weeks' duration, the first and third weeks with stovarsol, the second and fourth with emetine.
- b.* A course of three weeks duration, with 0.75 gram of stovarsol daily for a week, repeated after a week's interval.
- c.* For maintaining the effect, 0.25 gram daily for one to two months.

These authors found stovarsol was usually well tolerated and was only slightly toxic. Motile amoebae disappeared from the stools after four days and cysts were not seen after eight days.

van Steenis (74) gave stovarsol to 50 patients without seeing any toxic effect. In the beginning he used 0.25 gram twice a day for one week and repeated this after a week's interval. Later he replaced this treatment during the third week by 0.25 gram daily for three weeks. Of 15 patients followed for three to six months, 12 remained without symptomatic relapse or recurrence of amoebae in the stools.

Melnotte (54) treated 28 cases with daily doses ranging from 0.5 to 2.5 grams, interrupting medication frequently. Only 7 of his cases

could be followed for a longer period. With a dosage of 0.5 to 1 gram daily, 7 or 8 acute cases were "cured," one of whom relapsed the sixteenth day. One chronic case relapsed after the average dose of 9 grams used in this group. Of 19 patients treated with daily doses of 2 to 2.5 grams, 12 were cured, all of whom were recent cases who had never been treated before. Of 6 chronic or relapsing cases only 1 was cured. Melnotte believes that stovarsol prevents the formation of cysts. That he does not report any toxic effects with the dosage used is rather surprising.

Willmore and Martindale (85) found more relapses after stovarsol than after emetine, but combination of these two drugs proved more efficient than either alone. They believe that an idiosyncrasy to stovarsol exists in certain individuals, especially after repeated courses. At least one death has been reported. Toxic symptoms appeared in one case after 0.5 gram. They are using 1 pound of glucose in 1 quart of orange or lemon water daily as a minor precaution.

The results with stovarsol in the treatment of cases of acute and chronic dysentery and of carriers compare favorably with those following the use of any of the other drugs.

#### TREPARSOL

This pentavalent arsenical contains slightly more arsenic than stovarsol, according to the analyses of Flandin (23), which show that treparsol contains 28.75 per cent of arsenic and stovarsol 27.2 per cent, while neoarsphenamine contains 20 per cent. Flandin states that treparsol possesses advantages over stovarsol in the following points: (1) higher arsenical content, (2) more regular and slower elimination, beginning one day after its administration and completed in three days, while the elimination of stovarsol is irregular, (3) direct action on the parasite, since treparsol is decomposed with the formation of soluble salts in the intestines.

Flandin (23) feels that treparsol alone may act well in acute colitis but prefers to combine it with emetine. He gives a course of emetine for the first week and then for one to two months gives 0.25 gram of treparsol by mouth four times a day on the first four days of each week. Smaller doses are given to weak patients and to children. He found

immediate disappearance of motile amoebae and cysts. The final result was improvement in 80 per cent of his cases.

Garin and Lepine (26) recommend treparsol to be given in six or seven doses of 0.75 gram subcutaneously or, better, intramuscularly, either alone or in combination at first with emetine. In their experience motile amoebae and cysts disappeared rather slowly about the eighth day. They consider both stovarsol and treparsol most desirable drugs.

Vialard and Darl  gny (79) report 3 cases treated with emetine and treparsol. They believe they can give 0.75 to 1 gram a day.

### *Discussion*

The satisfaction which these compounds met at first has been marred by reports of arsenical poisoning, which seems to occur rather frequently after stovarsol. Treparsol is only slightly toxic. The chief symptoms are a skin rash, fever, vomiting, diarrhea, and visual and acoustic disturbances. Two patients developed symptoms after 0.25 gram of stovarsol (Schwartz (71) and Izar (33)), another after 0.5 gram (Willmore (84)). In the Peking Union Medical College Hospital there were four cases of poisoning among 37 persons treated with stovarsol. Among them was one death, after 4.75 grams, of a woman with amoebiasis who was invalided by severe septic polyarthritis. Eliminative measures, including the use of sodium thiosulphate, were of no avail.

Morgan (56), at the Conference of the China Medical Association in Peking in 1926, reported 3 cases of severe poisoning among 8 cases treated with stovarsol. The dose used at first was 0.75 gram of stovarsol a day, later this was reduced to 0.5 gram a day. The severest intoxication occurred after only 2 grams.

Manson-Bahr (50, 51) considers as safe not more than 0.25 gram of stovarsol daily for two weeks or not more than 0.5 gram daily for one week.

The sudden onset of poisoning without warning makes stovarsol very dangerous. Whether the precautions prescribed by Marchoux (52) and by Willmore (84) or the interruption of the medication every three days (Oppenheim (61)) will make it possible to avoid intoxica-

tion is uncertain The estimation of liver function and of the excretion of arsenic may possibly serve as a control

#### AURAMINE

Willmore and Martindale (85) have recently published preliminary observations on the treatment of amoebiasis with an aniline dye, auramine This substance is the hydrochloride of tetramethyldiamino-diphenyl-ketonimine, and has the formula  $(\text{CH}_3)_2\text{N} \cdot \text{C}_6\text{H}_4\text{C}(\text{NH} \cdot \text{HCl}) \cdot \text{C}_6\text{H}_4 \cdot \text{N}(\text{CH}_3)_2$  Fairbrother and Renshaw's (22) experiments showed that auramine killed paramacia in 15 minutes in a dilution of 1 20,000 Its phenol index is 40 Auramine killed twelve different organisms, including that of anthrax, in fifteen minutes in a dilution of 1 3000 and *Bacillus coli* in seven and one-half minutes in a dilution of 1 500

A compound of auramine with emetine was sought for oral administration and after some technical difficulties a dark maroon powder, stable and insoluble in water, was prepared This substance, for which the name auremetine has been suggested, is a combination of the hydriodide periodide of emetine and auramine and has approximately the following composition emetine 28 per cent, auramine 16 per cent and iodine 56 per cent

The low content of emetine, the constituent most poisonous for higher animals, is noteworthy This compound is very slightly decomposed by acids and alkalis, in contrast to emetine bismuth iodide Two grains by mouth caused vomiting in a cat weighing 3.6 kgm but was followed by rapid recovery The growth of amoebae was inhibited in dilutions as low as 1 100,000 The feces are orange-coloured after oral administration

Willmore (84) states that auramine has been practically free from any objectionable minor toxic effects, such as vomiting, nausea, abdominal pain or purging It is also much less depressing than emetine hypodermically and it is not necessary to keep the patient in bed Willmore considers bismuth subnitrate in massive doses (1 teaspoonful every three hours for several days and then three times a day for an indefinite period) a very valuable adjuvant He has never seen intoxication from this treatment

The method of using auremetine followed by Willmore since the summer of 1924 is roughly as follows, though, of course, it is modified to suit individual cases:

1. Acute cases, that is, those with blood, mucus, and amoebae in the stools, are given. (a) Auremetine, 1 grain, in a soft gelatin capsule four times a day after food, on alternate days for seven days, and then daily to a total of from 40 to 60 grains. (b) Stovarsol, 4 grains, three times daily for seven days, on alternate days with the auremetine. (c) On stovarsol days a rectal injection of 2 drachms of emetol (equal to 1 grain of emetine base) in 6 drachms of ether and 12 ounces of olive oil. (d) "Panama bismuth" every three hours for twenty days, and then three times daily.

2. Chronic or carrier cases are given. (a) Auremetine, and (b) stovarsol, on alternate days as described above, and (c) "Panama bismuth" three times a day before food.

3. When hepatic involvement is present 1 grain of emetine hydrochloride by intramuscular injection, on alternate days for six days (that is, 6 grains in all), may supplement or replace the emetol.

Of 40 patients thus treated 37 responded satisfactorily, that is, regained their health, lost all clinical signs of disease, including those present at sigmoidoscopic examination, and the stools were free from cysts for at least six months. These observations have the more value as having been made on the most severe and stubborn cases, the residue of pensioners infected during or before the World War, many of whom had passed through every dysentery center in England.

#### SUMMARY

From the reports of many workers presented here it can be understood how difficult it is to form an opinion regarding the value of these new remedies. Neither is the clinical picture of amoebiasis as yet sharply defined nor is its laboratory diagnosis developed to the level of that of other protozoan or bacterial diseases. We must consider the possibility of intrinsic differences in the virulence of different strains of *Entamoeba dysenteriae*, although we do not believe the evidence brought forward in favor of this theory to be sufficient by any means. That extrinsic factors such as climate, diet, and mode of life, acting on the host, may influence the clinical picture and course

of the disease admits little doubt. It is not astonishing that under these conditions the reports are at great variance, not only on account of the differences in the object but also in the mode of observation and in the training and equipment of the observers.

While amoebiasis is a public health problem only in badly sanitated countries of the warmer zones, an evaluation of the drugs available for use against it on the basis of their eradicating power can be properly done only in well sanitated centres, where no possibility of reinfection can interfere with the observations, and where equipment and highly trained personnel permit irreproachable application of all the available diagnostic and therapeutic methods.

All three types of remedies discussed in this review, according to experienced and reputable observers, have produced remarkable cures in a great number of cases resistant to any other form of therapy. It is not claimed that any of them is specific in its action and the more experience authors have, the more they abstain from premature enthusiasm.

Yatren is considered the drug of preference chiefly by German, Dutch, Japanese and South American physicians, who only occasionally combine it with emetine for acute cases. Many of them consider yatren superior to emetine. In the writer's experience yatren has given very satisfactory results, and during the last two years it has been used in the majority of about 175 cases of amoebiasis in this hospital. The use of emetine has been restricted to the comparatively rarer cases of acute colitis, in which it is used in combination with yatren, and of liver abscess.

Stovarsol and treparsol are used chiefly by French and North American physicians, commonly in combination with emetine.

In England, as Willmore (84) states, the general tendency is especially pronounced to centre the treatment of amoebiasis about emetine, which is used in doses smaller than those given formerly. Stovarsol has met very favorable and even enthusiastic comment. Opinion regarding yatren is divided, but the number of cases treated is small as yet.

The advantages of these three types of drug over the older therapeutic agents are evident. They are as a rule less toxic, more pleasant to

take, and produce, to use Willmore's (84) fitting words, "response to treatment" in a much higher percentage of cases

The disadvantages may be summed up as follows Yatren is a proprietary drug and hence the control of its purity and composition is left in the hands of a commercial enterprise The existence of a patent invites falsification and needless increase of price by traders, speculators and customs barriers Stovarsol and treparsol given alone are somewhat more frequently followed by relapses than yatren. Intoxication often occurs suddenly after small doses of stovarsol It is often severe and may even be fatal Experience with treparsol is limited but its toxicity is apparently slight.

Auremetine has so far been used only in 40 cases, though these were of the severest type and in the hands of unquestionable authority If combination with stovarsol turns out to be essential, this would have to be considered a disadvantage It is reasonable to hope that with the application of a satisfactory liver function test and with control of the elimination, the danger of arsenic poisoning from this drug would be removed or reduced

With regard to the eradication of amoebae, Willmore's combined treatment with auremetine, bismuth and stovarsol has stood the hardest test

In general usefulness yatren seems to be first, since it is the least toxic and the most widely applicable of all the remedies at hand. To determine the true significance of amoebiasis extensive investigations have to be carried out in which we are in need of the close cooperation of large groups of the population, whom we can advise to rid themselves of their amoebic parasites even if they should be harmless. Yatren provides us with the therapeutic test involving no risk.

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# THE ETIOLOGY OF PERNICIOUS ANAEMIA

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## HISTORICAL ETIOLOGICAL CONCEPTIONS

Combe, who described the first recorded case in 1822, saw no cause whatever. Elliotson wavered between an ill-defined notion of gravitational or emotional effect and one of a change to white-bloodedness. Addison who enjoyed the somewhat unique distinction of having propounded no hypothesis, merely wondered if fatty degeneration had anything to do with it. Fenwick considered the degenerative changes in the gastric mucosa to be significant. Perroud attributed the whole complex to fatty degeneration of the liver. Biermer felt that even in his cases of idiopathic origin, sufficient cause could be seen in the bad hygienic conditions, or in the diarrhoeas of his patients. The only lesions he could associate etiologically were ulcers of the colon. McKenzie believed that neurosis was a definite factor. Cohnheim, Ehrlich, and with them most of the early continental observers, regarded the marrow condition as the cause of the anaemia. The English school and many European authorities came to believe that blood destruction of abnormal degree was the means of blood depletion, and that the marrow changes were regenerative and compensatory.

The early bone marrow observations of Pepper, of Cohnheim and of Osler and Gardner resulted in emphasis being placed upon the abnormal type of blood formation seen and in the noting of phagocytosis of red corpuscles in this tissue. Ehrlich, who created haematology a science by the discovery of the value of aniline dyes for staining blood-smears, became especially interested in the presence of megalo-blasts in the marrow and the circulating blood. Whereas Cohnheim had been content to regard the marrow changes as a reversion to an embryonic type of blood formation and as of primary significance to the etiology, Ehrlich went a step further and conceived the marrow

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changes as degenerative in nature. This hypothesis of megaloblastic degeneration, rendered vivid by its author's classical stains of the blood tissues, substantially implanted itself in the minds of Ehrlich's contemporaries and has exerted a profound influence even to the present day. Ehrlich held up the megaloblast as a simple and infallible point in the diagnosis of pernicious anaemia and he embraced the inevitable and logical corollary that all anaemias showing megaloblasts were pernicious anaemia. This classification placed megaloblastic anaemias in a primary group and normoblastic anaemias in a secondary group, and ran parallel to Biermer's clinical classification, which permitted the term pernicious anaemia to be extended to several severe anaemias of known etiology.

The English school, before and during Ehrlich's studies, had developed a different viewpoint. Of first importance to the English investigators was an exclusive definition of the disease. Following in Addison's footsteps they applied the term pernicious anaemia only to cases of idiopathic origin, and excluded all cases, in spite of the blood picture, in which any cause was evident. To them pernicious anaemia was, at that time, largely a disease of the blood. The anaemia was primary and uncaused, and all other manifestations were the results of the anaemia. This fixed idea resulted commonly in the misinterpretation of newly discovered pathological facts. Bone-marrow changes (Pepper, Cohnheim) and gastric atrophy (Fenwick, Osler, Kennicutt) were not readily included among the manifestations of the disease but used as reasons for excluding the cases described from the pure "primary" class. In other words there was a tendency to attach etiological significance to any important pathological observation and to regard such observed cases as of a "secondary" nature. It became an international medical pastime to exclude cases from published reports on the basis of purity of type, each critic employing his own individual or local standards of judgment. The term "pernicious-anaemia" although used by Biermer to include several severe anaemias of known etiology, was adopted in England after 1874 but applied only to the idiopathic anaemia described by Addison. The net result of this conflict of conception and definition was the most glaring and sustained confusion which has ever clouded the history of a disease.

In any synoptic review of this most involved period (1870-1900) one

must recognize the stabilizing effect of the work of William Hunter, although it failed, in its entirety, to achieve the conclusive results which, in its beginning, it might seem to have promised. Its stabilizing effect lay chiefly in its direction toward other than purely haematological studies. Hunter emphasized the clinical signs and symptoms of the digestive system. Particularly his careful work on haemosiderosis of the liver has exerted a far-reaching effect on all subsequent thought. Briefly he demonstrated by gravimetric analysis that the liver in pernicious anaemia contains more iron than the liver in other anaemias. Siderosis had been little observed on the continent and, when found, had been frequently dismissed as due to iron medication and of no constant or specific importance. Hunter, on the other hand, held up hepatic siderosis just as stoutly as Ehrlich has held up the megaloblast, as an alleged specific finding. Then Hunter by a process of synthetic thought, which has always impressed the writer as at once natural but unwarranted, supposed that this deposit of iron-bearing pigment in the liver was the result of abnormal blood destruction in the portal area. He believed that a toxin, produced probably by a specific microorganism in the lumen of the intestine, was being absorbed into the portal blood and was there causing an intense destruction of blood corpuscles, the freed pigment from which was then deposited in the liver lobules. However little or much of truth may be contained in this hypothesis, it was the first, and it was a daring attempt to explain the anaemia by extensive blood destruction. Muir's study of the bone marrow in 1894 largely confirmed the morphological findings of the earlier investigators. But Muir, having been impressed by Hunter's insistence on the importance of alleged blood destruction, found it possible to interpret the marrow changes as a very extensive and energetic regeneration undertaken in response to a severe bodily demand for blood.

Thus were established two contending schools of thought. The one, initiated by Cohnheim and led by Ehrlich, taught that the anaemia was due to a primary alteration in the marrow, of the nature of an embryonic reversion, or, otherwise expressed, of a megaloblastic degeneration. This school approached the subject from an almost purely haematological angle. The other, initiated by Hunter, and supported by Muir, taught that abnormal blood destruction was the



essential fundamental process, and that the extreme marrow changes were to be regarded as a compensatory regenerative activity in response to an urgent physiological need. This school approached the subject from a physiological and clinical, as well as a haematological angle.

Many observers, notably Mott, while willing to admit abnormal blood destruction to a degree, believed that it depended upon the circulation being presented with inadequately formed corpuscles. They therefore regarded abnormal blood formation as fundamental and abnormal blood destruction as a consequence.

The importance of the digestive system became apparent through the combined work of Fenwick, Flint, Barclay, Hunter and others during the period 1852-1890, with particular emphasis on the atrophy of the gastric mucosa, the specific glossitis and the familiar train of gastro-intestinal symptoms. From 1884 onward to the present, the importance of the nervous system has become increasingly clear, due to the work of some 50 observers. Whereas until the early nineties the disease was regarded generally and chiefly as a blood disease, it is now of necessity regarded as a much wider tissue involvement, the blood features being but one of three outstanding system changes.

Within the historical period, as here briefly outlined, may be detected the issues which remain today. The chief issue is the problem of the relative importance of abnormal blood destruction and abnormal blood formation, and is a problem involving a close scrutiny of all the haematological data in our possession. It further involves an etiological evaluation of other manifestations of the disease, of other possible related factors, a comparison with other similar clinical anaemias, and a critical review of experimental findings.

#### EVALUATION OF THE HAEMATOLOGICAL DATA

The typical, fully-established blood condition is a very severe anaemia, of which marked oligocythaemia and high individual corpuscular complement of haemoglobin are two characteristic features. Morphological alterations in the red blood cells stand out as the most highly characteristic feature. A marked degree of anisocytosis, rendered so graphic by the now familiar Price-Jones charts, is constantly present and depends upon the presence particularly of macrocytes and

megalocytes and also, but to a less degree, of microcytes. The macrocytes are moreover characteristically of an oval rather than a circular contour. Among the cells of normal or subnormal size, poikilocytosis is commonly present in a more or less marked degree. The shapes exhibited are somewhat characteristic of the disease viz., forms resembling Indian arrow heads, Grecian urns, dumbbells, as well as unsymmetrical figures impossible to describe. The white blood cells are reduced, with absolute reduction in the polymorphonuclear neutrophils. The blood platelets are markedly reduced in number.

Nucleated red blood cells,—normoblasts and megaloblasts,—while characteristic and to some degree diagnostic when found, occur much less frequently than formerly taught. In the blast crises, when occurring in high percentage, they are not usually of good prognostic significance, although when occurring in less numbers, especially in conjunction with increased numbers of reticulocytes and polychromatic corpuscles, they are of good prognostic significance.

The disturbed state of the bile-pigment metabolism may be briefly summarized as follows: hyperbilirubinaemia, increased output of urobilinogen and urobilin by the liver, and increased output of urobilin by the kidneys. In addition to these changes, there is a deposit of iron-containing pigment in the spleen, the kidney and particularly in the liver. The bilirubin of the blood is apparently fixed in some physico-chemical union with the plasma proteins so that it does not readily dialyze. The peculiar jaundice of grape-fruit hue, when present, is due to staining of the tissues by this bilirubin. Blankenhorn shows that hyperbilirubinaemia may sometimes be present without jaundice. Moreover, considerable anaemia may be present without any marked hyperbilirubinaemia but, as a rule, severe anaemia is accompanied by definite increase of this pigment in the plasma. Minot has indicated that the simple observation of the degree of staining of the plasma is a fair index to the severity of the anaemia and may be rendered of comparative value by determining how much water must be added to the plasma to cause the colour to disappear. Van den Bergh has shown that this plasma bilirubin behaves differently in the diazo reaction from the bilirubin associated with hepatic obstruction.

The pigmentary increase in the bile and urine, as well as the occurrence of siderosed cells in the urinary sediment, are further evidences

of the disturbed pigment metabolism. It is not perfectly certain that they result from abnormal blood destruction.

Sellards and Minot have shown that patients with pernicious anaemia will excrete haemoglobin in the urine when injected intravenously with doses of aqueous solution of this pigment which cause no such excretion in normal individuals or in patients with haemorrhagic anaemia. In very severe cases of pernicious anaemia free haemoglobin may be found in the serum. The urine will show characteristic absorption bands of haemoglobin on spectroscopic examination more frequently than supposed.

Peabody and Broun, as a result of a comparative study of the vertebral bone marrow in pernicious anaemia and other diseases, as well as in persons killed by traumatism, and with particular reference to the phagocytosis of erythrocytes by the clasmatoocytes, found that in pernicious anaemia bone-marrow a degree and an acuteness of phagocytosis occurred, sufficient to suggest that this process of blood destruction may be a factor in the production of the hyperbilirubinaemia.

Custom during the past twenty years has classified the haematological data in somewhat the following manner:

- A. *Evidences of abnormal blood destruction* the oligocythaemia, the small microcytes, fragmentation forms of erythrocytes, the phagocytosis of corpuscles by the clasmatoocytes, the deposition of haemosiderin in various organs, and the several other signs of disturbed pigment metabolism just recorded.
- B. *Evidences of abnormal blood formation* the macrocytes and larger microcytes of the circulation, as well as the occurrence of nucleated red blood cells, especially megaloblasts.
- C. *Evidences of blood regeneration* the occurrence of immature red corpuscles,—polychromatic cytoplasm, nucleated erythrocytes, reticulocytes, and rising figures both for the red blood cells and the haemoglobin percentage.

One of the most striking statements which it is possible to make in connection with the problem of blood destruction is this: the only site and the only mechanism of blood destruction which has been demonstrated is the phagocytosis by the clasmatoocytes of the reticulo-endothelium, especially in the bone marrow. Osler and Gardner could not suppose this to be of any specific importance since they observed an apparently equal phagocytosis in the marrow in some cases of pneumonia. Peabody and Broun found a very abnormal increase in phagocytosis in certain cases dying of hepatic cirrhosis, pneumonia, typhoid

fever, and tuberculosis. However, the most marked instances were encountered in patients dying in an acute stage of pernicious anaemia. On the other hand, in the case of a patient dying in a remission of this disease, phagocytosis of red blood corpuscles was not a striking phenomenon.

The problem of whether the erythrocytes so engulfed are effete corpuscles is not settled. The phagocytosis is apparently an acute and active process because haemosiderosis, characteristic of a more sluggish phagocytosis, is practically absent in the marrow of pernicious anaemia. The greater problem as to whether or not this phagocytosis can account for the degree of oligocythaemia present is also impossible to settle, but from comparison with other diseases, in which great phagocytosis occurs without a corresponding degree of oligocythemia, the answer may be temporarily given in the negative.

The degree of bilirubinaemia corresponds roughly, and in a direct manner, to the degree of oligocythaemia, so that both are greatest and both are least at the same time in the disease. As the erythrocyte count and haemoglobin percentage rise in a remission, not only does the degree of bilirubin in the plasma decrease, but there appear the accepted evidences of regeneration, and the red blood corpuscles show a more normal type of formation. Conversely, when a relapse occurs, the erythrocyte count and the haemoglobin percentage fall, the degree of bilirubinaemia increases, and the red blood corpuscles exhibit increased evidence of abnormal formation. Generally, therefore, there is to be noted an undivorceable relationship among the three features, which custom has separately recognized, viz., abnormal blood destruction, abnormal blood formation, and blood regeneration.

As Archibald and as Minot and Lee have pointed out, it is possible to recognize five somewhat distinct types of the disease, depending upon the balance maintained between blood destruction and blood regeneration. In the first there occurs a rapid unremitting course with oligocythaemia, marked degree of abnormal blood formation and of bilirubinaemia. In the last there occurs a long monotonous course with much evidence of abnormal blood formation and a less degree of bilirubinaemia,—the so-called myelotoxic cases. Between these extremes there lie three types of remitting cases. The middle type of the five is one in which may be synchronously observed evidences of ab-

of the disturbed pigment metabolism It is not perfectly certain that they result from abnormal blood destruction

Sellards and Minot have shown that patients with pernicious anaemia will excrete haemoglobin in the urine when injected intravenously with doses of aqueous solution of this pigment which cause no such excretion in normal individuals or in patients with haemorrhagic anaemia In very severe cases of pernicious anaemia free haemoglobin may be found in the serum. The urine will show characteristic absorption bands of haemoglobin on spectroscopic examination more frequently than supposed.

Peabody and Broun, as a result of a comparative study of the vertebral bone marrow in pernicious anaemia and other diseases, as well as in persons killed by traumatism, and with particular reference to the phagocytosis of erythrocytes by the clasmatoocytes, found that in pernicious anaemia bone-marrow a degree and an acuteness of phagocytosis occurred, sufficient to suggest that this process of blood destruction may be a factor in the production of the hyperbilirubinaemia.

Custom during the past twenty years has classified the haematological data in somewhat the following manner

- A *Evidences of abnormal blood destruction* the oligocythaemia, the small microcytes, fragmentation forms of erythrocytes, the phagocytosis of corpuscles by the clasmatoocytes, the deposition of haemosiderin in various organs, and the several other signs of disturbed pigment metabolism just recorded
- B. *Evidences of abnormal blood formation* the macrocytes and larger microcytes of the circulation, as well as the occurrence of nucleated red blood cells, especially megaloblasts
- C *Evidences of blood regeneration* the occurrence of immature red corpuscles,—polychromatic cytoplasm, nucleated erythrocytes, reticulocytes, and rising figures both for the red blood cells and the haemoglobin percentage

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as tested by Bauer's galactose and Strauss's levulose tests, while the sulpho-conjugation test indicated a deficiency in detoxication function

#### ETIOLOGICAL EVALUATION OF OTHER MANIFESTATIONS

Among the manifestations, other than haematological, which appear to bear a specific relationship to the disease, the following are to be particularly designated glossitis, achlorhydria, nerve tissue degeneration, the fatty changes and the remissions. In addition the general metabolism requires description. All other symptoms and signs will be purposely neglected as not bearing either constant or apparent specific relationship.

What is written of the glossitis may be applied to the stomatitis, pharyngitis, oesophagitis and even gastritis, which the symptoms indicate may co-exist as the apparent extension of the same process. Noted first by Barclay in 1852, and its incidence later somewhat over-emphasized by Hunter, the glossitis has now been granted a specific relationship to the disease. No one except Percy has supported Hunter's contention that glossitis occurs in every case. Panton, Maitland-Jones and Riddoch found it in 25 per cent or slightly higher. In the early active stages the tongue, always clean and moist, may present a fiery red carmine hue, a painfully fissured dorsum, and sometimes vesicles containing serum. Later when the organ is anaemic, the glossitis is manifest chiefly by a mottled red appearance along the borders or in patches of hyperaemia on the surfaces. Small ulcers may be seen. In the final stages of the disease the process is usually less noticeable, the tongue presenting, in general, an ironed-out, atrophic appearance. The papillae are dwarfed or absent. While comparatively quiescent, the glossitis may occur in periodic attacks of soreness and marginal redness, even in the late stages. In patients with very long remissions of the disease, the atrophic tongue remains as a permanent hall-mark, of equal significance to the permanent macrocytosis which is likewise frequently noted.

The glossitis is troublesome in varying degrees in different cases showing it, and interferes with eating, sometimes with sleeping. It is not infrequently the initial symptom of the disease. Local treatment fails to benefit it. During the disease it is characterized by an irregu-

lar periodicity A troublesome glossitis reappearing or recrudescent during a remission often indicates the nearness of a relapse

At autopsy, the tongue shows the gross and microscopic features of a combined mucosal and muscular atrophy At points where the mucosa has disappeared a round-cell infiltration will be found in the submucous tissues In severe cases a great proportion of the muscular fibres are replaced by fatty connective tissue Hunter obtained from the interior of such tongues pure cultures of a virulent long streptococcus and considered this microorganism to be responsible for at least part of the glossal manifestations The periodicity of the symptom, glossodynia, suggests that any causative microorganism would be characterised by its tendency not only to cruesce and subside, but also to migrate downward and cause the oesophagitis and gastritis so frequently associated No specific microorganism has been isolated from the tongue lesions The nature of the glossitis is obscure Faber would interpret the glossitis as due to a chronic toxaemia with the hypothetical poison responsible at once for all the digestive, nervous and blood abnormalities It is of interest to recall the occurrence of glossitis in sprue and pellagra, between which two forms Wood notes a great difference, and both of which apparently differ from that in pernicious anaemia No one has definitely noted glossitis in so-called "pure" cases of subacute combined degeneration of the cord, but it is thought to occur in these cases even in the absence of blood changes

*Achlorhydria* Von Noorden, Einhorn, Stewart, Grawitz, Martius and others were first responsible for the chemical examination of the stomach contents (1890-1897) and for thus affording to clinical medicine a physiological means of study which has since proved of greater value than anatomical or histological means, especially with reference to pernicious anaemia Grawitz in the late nineties listed "achylia gastrica" as an etiological factor in the broad group of cases which he, in conformity with continental custom, included under the term pernicious anaemia Among Martius' 17 cases of "achylia," reported in 1897, 2 died of pernicious anaemia and showed, post-mortem, pronounced atrophy of the gastric and intestinal mucosa He took the attitude that while arrest of gastric secretion arising from mucosal



stitutional or acquired In such a grouping the acquired forms might be listed as follows (1) Alcoholic achlorhydria (2) The achlorhydria resulting from gastroenterostomy Hurst found a case at Guy's Hospital illustrating this syndrome, but achlorhydria due to regurgitation of alkaline jejunal contents might be apparent rather than real. (3) The necessary achlorhydria resulting from complete gastrectomy Hurst claims to know of 5 cases in which pernicious anaemia followed extirpation of the stomach As Piney pointed out, since this operation is usually undertaken for carcinoma, any subsequent alleged pernicious anaemia would require to be carefully studied with special intent to rule out a secondary deposit of carcinoma in the bone marrow (4) The achlorhydria of gastric carcinoma The fractional method in cases of stomach cancer shows achlorhydria in 50 per cent, although in the other 50 per cent the amount of free HCl is greatly reduced Hurst has seen typical subacute combined degeneration associated with cancer of the stomach, in which achlorhydria was present Clinicians are all familiar with the occasional association of true pernicious anaemia with cancer of the stomach, although this double diagnosis must be made with care, since there occurs a macrocytic but not Addisonian anaemia not infrequently in such cases.

Accepting as bonafide all such cases of pernicious anaemia occurring in instances where the achlorhydria might be conceived of as being acquired, there remains a major objection to admitting acquired achlorhydria as a predisposing cause of pernicious anaemia. The instances reported are so few that this group might be supposed to have been potential victims of pernicious anaemia in the course of ordinary events, and there is no proof given that they did not have achlorhydria previous to those events from which they are credited with having acquired it The balance of collected evidence favours the view that the achlorhydria of pernicious anaemia is a condition long antedating the beginning of the disease

Among the causes which have been alleged for the achlorhydria may be noted the following (1) *The anaemia* This conception grew up during the initial confusion of the subject, but has been completely set at rest by facts already set forth, viz, that achlorhydria antedates the anaemia, and persists, unaffected, during long periods of blood improvement In Hurst's gastric studies in cases of haemorrhagic and

other simple anaemias, the curve of secretion was found perfectly normal (2) *The toxic or infective processes which likewise cause the other symptoms of the disease* In the light of this theory the achlorhydria is the functional result either of a toxic parenchymatous gastritis due to the prolonged insult of small concentrations of toxin over a long period, and therefore parallel to our own conceptions of other parenchymatous intoxications, or, of an interstitial infectious gastritis resulting, by condensation of fibrous tissue, eventually in atrophy of the secreting glands In favour of this theory is the fact that 20 to 30 per cent of patients show a prodromal debility, for years previous to the disease, characterised by marked digestive tract disturbances Against it is the fact that 70 per cent of patients have been healthy until the onset of the disease (3) *Constitutional factors of unknown nature* This hypothesis supposes that achlorhydria is a functional phenomenon not necessarily associated with any gastritis The biopsies of Hurst and Passey revealed that the gastric mucosa in pernicious anaemia may be histologically normal, although achlorhydria was present In some cases at least, therefore, we have the phenomenon of normal architecture associated with absence of function Again, as Hurst (1923) has reasonably argued, a non-functioning gastric mucosa is for several reasons more liable to secondary injury than a functioning one Food matter fails to receive the normal gastric maceration and is hence more liable to cause mechanical irritation The mucosa, robbed of its normal antiseptic defence, is prone to infection from bacteria-laden food and saliva from the notoriously unhealthy mouth

This theory regards the achlorhydria as caused by some "primary" fault, perhaps some constitutional and even inherited abnormality It regards the manifestations of gastric sepsis as due to secondary injury and invasion That a constitutional or even hereditary factor may be all important is strongly suggested by the study of true instances of familial pernicious anaemia In such instances the only tangible link between affected blood relatives is the achlorhydria Hurst phrases this the "achlorhydric gastric diathesis" and recites many instances of achlorhydria in the blood relatives of pernicious anaemia patients In some instances an absence of gastric secretion

has been found in patient's children as young as 6 and 4 years of age, thus strongly suggesting that the condition is an inherited one

While clinical study has not elucidated the cause of *achlorhydria* it has distinguished between it and the condition properly named *achylia gastrica*. In England and North America the former term, and on the continent the latter term are used somewhat promiscuously to indicate either condition. The distinction between the two is apparent from the following definitions. Achlorhydria is a condition in which by the use of the fractional test meal, no free HCl is detected in the stomach contents during either the digestive or interdigestive period, although combined acid and some degree of peptic activity are found. Achylia gastrica is a condition in which, when similarly examined, neither free nor combined HCl is detected at any period, and peptic activity is lacking. The latter definition, if desired, may be rendered more strict by specifying lack of response to histamine and gastrin and inability of the mucosa to secrete neutral red. True achylia gastrica is a rare condition. Either condition may be found in pernicious anaemia—usually achlorhydria. The distinction between the two is one of degree of failure of the gastric secretory function. The former is an instance of relative, the latter of complete delinquency of physiological function.

There is a tendency to dismiss the subject of achlorhydria with an unjustified assumption that the condition is due to the absence of an unrecognized hormone, or to suppose that it is part and parcel of a metabolic disturbance of some substance as, for example, the chlorides. What has physiology to offer in explanation of this phenomenon?

Present conceptions of the physiology of gastric secretion are based on the work of Pavlov, Edkins, Carlson, Ivy and others. Ivy (1925) would divide stomach digestion into three phases. (1) The cephalic stage, which corresponds to the psychic stage of Pavlov but includes the operation of lower brain centres than the cortical. (2) The gastric phase, which includes the mechanical and chemical influence of food on the stomach. (3) The intestinal phase, during which gastric secretion is aroused by contact of HCl, digested foods, soaps and other substances with the duodenal mucosa. Edkin's work on gastrin sounds the key-note to present investigations which are largely con-

cerned with establishing a humoral mechanism. Edkin's gastrin was extracted from pyloric mucosa by weak acid, peptone, or partly digested protein solutions. Similar substances may be extracted from many tissues. That from hog's stomach and duodenum was shown by Ivy and Fisher to resemble insulin in its lowering of blood sugar, while insulin, on the other hand, does not stimulate gastric secretion. Rogers and his associates made extracts from various organs, administered them subcutaneously and found that those from thyroid, parathyroid, liver and pancreas definitely stimulated gastric secretion, while others did not. But these extracts showed other physiological activities as depressors and as smooth-muscle excitants, each with effects peculiar to itself. They felt unjustified in assuming the existence of any specific hormone acting only on the stomach, although a common element in their various extracts seemed to act as such. In Ivy, Lim and McCarthy's cross-circulation experiment between two Pavlov pouch dogs, by feeding the one and noting the gastric secretion from the other, a definite suggestion of a circulating gastric stimulant, appearing late in digestion, was obtained. Ivy and Farrell were next successful in transplanting a stomach pouch into the mammary tissues of a female dog and in showing that in this miniature stomach, separated as it was from nerve supply, there appeared an acid secretion at a period some hours after a meal. This furnishes incontestible evidence of the operation of a humoral mechanism, depending probably on circulating food substances. The secretion of gastric juice is therefore a physiological activity for the production of which nervous, mechanical and humoral factors have been established, but for which no definite hormone has been found.

The clinical and pathological studies of human gastric disease teach the one great lesson that the stomach is a barometer indicating the general condition of well-being or cachexia. Cancer, irrespective of the location of the tumour, is associated with hypoacidity and anacidity in direct proportion to the development of the general cachexia. Carlson believes that the hypoacidity of pellagra and beri-beri is an expression of the cachexia of diet deficiency. Achlorhydria is frequently found in the toxæmias of pregnancy and is always present, so far as critically reported, in the acute haemolytic anaemia of pregnancy which bears so close a blood resemblance to pernicious anaemia.

Faber has shown that of all the cases of *Dibothriocephalus latus* infection which develop the pernicious-like anaemia, only 25 per cent have normal gastric acidity, many of them showing achlorhydria. Achlorhydria is liable to be found associated quite frequently with the following conditions,—exophthalmic goitre, arthritis deformans, cholecystitis and appendicitis. As will be presently emphasized it may, and in fact usually does occur, without association with any disease. Faber and Gram have made a definite recognition of a severe, simple anaemia, with low colour index, red corpuscles smaller than normal, fluctuant in character and temporarily relieved by iron, which may accompany achlorhydria whether the achlorhydria is uncomplicated or is complicated by exophthalmic goitre, or arthritis deformans.

Achlorhydria has not been produced experimentally by any purely physiological means. When produced by intoxications or by prolonged drainage of a gastric fistula, it does not appear until the general cachexia would seem to demand it.

While we are in ignorance of the cause of achlorhydria, we are equally in ignorance, so far as accurate knowledge is concerned, of its consequences.

Such symptoms as anorexia, persistent painless regurgitation, feelings of distention, and chronic recurrent diarrhoea, might be attributed to achlorhydria except that achlorhydria so commonly exists without them. Achlorhydria apparently results in disturbances of the intestinal flora of equal degree whether in pernicious anaemia or in uncomplicated cases. These changes in the intestinal flora will be mentioned later. From the fact that free HCl is recognized as an essential intermediary in the stimulation of the pancreatic juice, it might be expected that a condition of achylia pancreatica would result. The investigations of Hurst and of McClure et al indicate, however, that the pancreatic function is normal both as regards enzyme secretion and alkaline fluid secretion. Achlorhydria exerts a definite influence on the acid-base balance of the blood, as proved by the numerous investigators, from Schittenhelm to Ackman, of the phenomenon of the "alkaline tide" of the urine. The degree of alkaline tide varies directly with the degree of acidity in the stomach, being absent or diminished in cases of achlorhydria and completely absent in cases of true achylia gastrica.

Whatever its causes or consequences may be, achlorhydria is almost invariably associated with pernicious anaemia

The converse of this statement, however, is not true Achlorhydria may exist, and usually does exist, without pernicious anaemia Bennett and Ryle found achlorhydria in 4 per cent of 100 medical students of an average age of 20 years Wright found achlorhydria in 1.6 per cent of 250 children between the ages of 6 and 15 years Faber estimated that of all achlorhydric individuals 10 per cent develop pernicious anaemia Among the other 90 per cent some may suffer from comparatively less fatal diseases,—exophthalmic goitre, arthritis deformans, appendicitis, cholecystitis—although the majority remain in good health

It would seem advisable to adopt the following tentative conclusion Achlorhydria, a functional abnormality of constitutional origin, is almost invariably associated with pernicious anaemia, and forms, in these cases, a necessary link in an etiological chain, to which by the addition of further unknown links, pernicious anaemia is made to appear

*Nerve tissue degeneration* Since Lichtenstern's report of posterior column degeneration associated with pernicious anaemia in two cases diagnosed as tabes, but which were probably cryptogenic pernicious anaemia, the subsequent studies of Lichtheim, Putnam, Dana, Von Noorden Eisenlohr, Minnich, Russel, Batten and Collier, and many others have established the occurrence of combined system degeneration in association with pernicious anaemia Since 1910 the combined work of the Dejerines, Crouzon and Jumentie, of Cadwalader, Schaller, and others have resulted in better understanding of the nervous system signs and symptoms Woltman has demonstrated the occurrence of brain lesions similar to those in the spinal cord Hamilton and Nixon have studied the sensory phenomena in particular and made the important observation of the commonness of peripheral nerve degeneration

Pathologically, the nervous system in a well-developed case, shows wide changes Posterior and lateral column degeneration, in varying proportion, definite cerebral degeneration running more or less parallel to the degree of cord involvement, and wide spread peripheral nerve degeneration constitute the phenomena These degenerations occur

in the myelin sheaths of long nerves and long tracts, being stained by Weigert's method, and have suggested to Woltman the operation of a toxin. Collier has noted the absence of neuroglial increase following these lesions, a fact which gives them a unique position in nervous degenerations. Piney (1925) noting this, has viewed the alterations as illustrations of abiotrophy.

During remissions of the disease no improvement occurs in objective nervous signs, although the process frequently becomes quiescent. The disharmony noted between symptoms and pathological cord findings is to be explained, according to Hamilton and Nixon, on the basis of the peripheral nerve degenerations. Blankenhorn has suggested that bile salts in the blood might be seriously considered as the cause of the nervous degenerations, since bile salts may be found in the blood in cases showing definite nervous involvement but comparatively little anaemia.

The obtrusive sensory symptoms of numbness and paresthesia may constitute the first indications of the disease. Marked objective signs may develop rapidly without any anaemia, or more slowly without anaemia, and continue for years in a chronic course without anaemia until terminally, when the specific type of anaemia appears. The commonest type of case is one in which the nervous manifestations begin some months after the onset of the anaemia with weakness. In later stages of pernicious anaemia the true state of the patient is more related to nervous changes than blood changes. A patient may die with a fair blood level maintained. The presence of nerve changes always indicates a more severe phase of the disease than when blood changes are alone present.

While this type of cord change,—combined system degeneration—occurs much more commonly in pernicious anaemia than in all other conditions combined, it is not to be forgotten that very similar changes may be found in poisoning with lead, arsenic, ergot, chick-peas, alcohol (chronic), and tea; and in shick, pellagra, diabetes, leukaemia, diphtheria, Addison's disease of the suprarenal capsules, tuberculosis, syphilis, typhoid, carcinoma, senility, chronic jaundice, malaria, influenza, scarlet fever, tetanus and pregnancy.

*The fatty changes* These affect chiefly the heart. In fact pernicious anaemia is the only disease in which very marked fatty degen-

eration of the heart muscle occurs. The liver and kidneys are also not infrequently involved. These familiar facts must be merely stated because of their probable specific relationship to the fundamental process of the disease, although their nature is obscure.

*The remissions.* A remission is a spontaneous blood improvement characterised by general symptomatic improvement. Panton et al found that 85 per cent of cases showed remissions and 15 per cent did not. The remissions are subject to no known laws with regard either to their rapidity of onset, their duration, or their excellence, in any given case. The excellence of a remission may be judged by its duration, the degree of strength regained, the degree of blood regeneration and the degree of disappearance of morphological abnormality on the part of the blood corpuscles. The objective nervous signs do not improve, although nervous involvement does not often increase during remissions. Glossitis frequently continues during all but the most excellent remissions.

A remission is probably a period of comparative freedom from the operation of the causal process, rather than a period of bodily reactive improvement in the face of continued disease. Nevertheless the natural recoverability of all tissues (except the nervous which do not improve) may be seen to be less and less with each subsequent remission, for, although exceptions occur, there is to be noted a downward gradient when the remissions in any one case are compared.

While the health of the patient, in the earlier stages of the disease, may be said to follow roughly the haemoglobin level, there occurs a definite disruption of this relationship later on, for patients may die while their blood remains at a comparatively satisfactory level. In the latter stages the true condition of the patient is better expressed in terms of the nervous system involvement.

If our conception of the cause of the disease is that of an active destructive agent, then a remission would rationally be regarded as a period during which this agent was either absent or in comparative abeyance. If our conception of the cause of the disease is that of a deficiency of certain factors vital to metabolism, then a remission would rationally be regarded as a period during which these factors are replaced. In either case a fluctuating mechanism is apparent. Furthermore, it is to be observed that whereas the blood system and



nervous system are affected by remissions, the former positively and the latter negatively, the digestive system retains at least one unaffected principle—the achlorhydria

*The general metabolism* Omitting references for the sake of brevity, the following points are selected from the mass of somewhat discordant findings. There is no evidence of any abnormality of carbohydrate metabolism. So far as lipoids are concerned, there is a recognized depletion of blood cholesterol during severe phases of the anaemia, and usually a high ratio of unsaturated fatty acids in the blood though not to a distinctly pathological degree, a satisfactory usage of fat eaten, and no evidence of abnormal metabolism of simple fats, although there is a tendency to over-storage of fat, and a tendency also to the pathological infiltration by fat in active tissues. Concerning protein metabolism, there is a tendency to a negative nitrogen balance; amino-acids are increased in the blood and the urine shows double the normal amount of oxyproteic-acid nitrogen. Blood creatinin is increased. In this connection the extreme muscular wasting, especially in cases of marked cord involvement should be borne in mind. Any increased protein catabolism is probably an expression of the cachexia, as in that of carcinoma and syphilis. The usually high uric acid nitrogen suggests that the purine metabolism requires further study especially in view of the benefits derived from feeding with glandular organs. The metabolism of iron has already been discussed. There exists a tendency to chloride retention although there is no evidence that an abnormality of the chloride metabolism plays any important rôle in the disease. Studies of the basal metabolic rate have served to suggest that the use of energy is determined by two opposing factors: (1) a positive stimulation connected probably with increased blood production, (2) a retarding influence due to the tendency to storage and infiltration of fat

#### ETIOLOGICAL EVALUATION OF OTHER POSSIBLY RELATED FACTORS

*The type or constitutionality of the patient.* This problem involves a description of certain alleged constitutional factors common to these patients and some reference to familial pernicious anaemia. Addison noted that the disease occurred “chiefly in persons of a somewhat large and bulky frame.” Maitland-Jones as well as Levine and Ladd have

noted the great frequency of gray or white hair Sheard among 15 cases found but one exception to this apparent rule In the 14 cases showing the feature, he determined that the average age at which grayness commenced was 29.4 which was 15 years prior to the average of the onset of the disease He further noted, as others have, the frequency of "silky" or very fine soft hair

Achlorhydria is of course the most striking feature of the disease which could be interpreted as a constitutional one Bassler and Gutman, in studying the constitutionality of achlorhydric individuals, have placed them in the "adrenotype" group,—females of masculine build, males of the apoplectic diathesis, with tendency to pigmentations, very firm and stained teeth, and great mental susceptibility to external influence

Anthropological measurements of a most painstaking character have been made by Draper on 45 cases of pernicious anaemia For a full understanding of his motives and methods reference should be made to his book As compared with similar measurements in other disease groups (gall-bladder, gastric and duodenal ulcer, asthma, nephritis and hypertension, and pulmonary tuberculosis) Draper found as follows people with pernicious anaemia have short broad faces, large mandibular angle, very short noses, short but deep, wide chests, especially wide subcostal angles, and (especially the males) very long thin ears "The male of the pernicious anaemia race, therefore, is a medium to tall individual with short chest, high place umbilicus, long abdomen, and a tendency to eunuchoidal habitus as shown by his relatively long lower extremities The males of this group show definite feministic tendencies in the domain of the secondary sex characteristics But the skeletons show average or greater sex divergence in the growth of the long bones In this case the convergence of sex insignia upon the so-called intermediate form is more marked than in any other disease group This may be reflected in the wider pelvis of the male of the pernicious anaemia group" In commenting upon Draper's work, Stockard says in part, "The pernicious anaemia group tended in their measurements very decidedly to approach the acromegals They had very large subcostal angles and had an average profile that tended toward the acromegalic picture The anaemic persons may by some possibility be a peculiar deviation from the bone

growth state of the acromegalics Both conditions may have some connection with calcium metabolism, and blood disturbance and bone disturbance in this way may be somehow interrelated "

Stockard favours the view that type differences are evidenced by marked variation in anatomical measurements but that constitutional differences may exist in members of the same type and be due to such influence as the endocrine glands, so that while type is permanent, constitutionality may vary, even in an individual. Further work by Draper, especially on the physiological, psychological, and immunological aspects of the members of these disease groups will be awaited with interest A possible result of such investigations may be the division of people into species or subspecies

Sufficient has been written to indicate that there exists some reason why investigators and writers on pernicious anaemia should suspect that these patients may possess at least a definite peculiarity of constitution if not of type.

Minot (1927) informs the writer that Palmer Howard was first to note the *familial occurrence* of pernicious anaemia Klein in 1891 saw the disease in 3 brothers and sisters Byron Bramwell a little later described a family in which 7 individuals in two generations had suffered from pernicious anaemia. Since then the phenomenon has been noted by Caccini, Schauman (1894-1917) Gulland, Cabot, Osler (1914), Gilbert and Weil, Patek, Willson, Andree Bartlett, Roth, G R. Minot, Piney, Matthes and others Schauman by 1918 had collected information of 24 families in which there was noted hereditary occurrence of either idiopathic pernicious anaemia or of the "pernicious anaemia" due to dibothriocephalus, or of both of these in the same family. More recent confirmation of familial occurrence has come from the reports of Levine and Ladd, Meulengracht, Gram, v. Decastello, Mustelin, and Gilford. Meulengracht (1925) has considered the technicalities involved in an hereditary study of pernicious anaemia Hurst has collected many instances in which achlorhydria has been found among the blood relations of patients with pernicious anaemia, strongly suggesting that the obvious link in the chain is the absence of gastric secretion. Piney distinguishes between megaloblasts with reticular nuclei and those with "cart-wheel" nuclei, and contends that the former or true variety are found only (apart from the

embryo) in pernicious anaemia and acholuric family icterus, the "two diseases of the blood" in which family incidence is well recognized. He noted in his own cases a frequent history of the patient not having been a full term infant. Piney believes that the abnormal type of blood formation in pernicious anaemia is an embryonic reversion, due to inherited propensities of the individual, and possibly related to the constitutional achlorhydria. The nervous tissue degenerations he would interpret as an abiotrophy. Finally he suggests the working hypothesis, with which all cannot of course agree, that the various agents capable of producing a "secondary" anaemia in ordinary persons will produce pernicious anaemia in such individuals as possess the necessary remnant of megaloblastic tissue. This is practically Cohnheim's hypothesis reinforced by distinctions between two alleged types of megaloblasts and by observations on the family incidence. Barker (1926) has recently considered the hereditary factors and stated the possibility of the view that pernicious anaemia is a genotypic disease, possible only in biotypes, but requiring for its development, certain "releasing factors" in the environment. He comments on the difficulties of applying the method of statistical summation and offers three reasons why the disease may be absent in families where it might be expected to occur under the inheritance theory: (1) It is a disease of later life, many potential candidates dying before it can become manifest. (2) Many cases are overlooked. (3) The possibility that the "releasing factors" have not been operative upon these individuals.

The genotypic conception of pernicious anaemia is at present of little more than academic interest and whether it eventually proves convincing or otherwise, ordinary pathological studies must be pursued to determine the sequence of events in the pathogenesis.

*The food factor* The voluminous work on vitamins during the past decade unquestionably suggested that avitaminosis might play some rôle in pernicious anaemia. Falconer concluded that blood changes in vitamin A deficiency were neither striking nor constant enough to constitute specific deficiency lesions. Koessler et al. do not indicate the condition of pigment metabolism in the anaemia they produced in rats by chronic vitamin A deficiency, and hence any comparison with pernicious anaemia, lacking this information, is at once problem-

atical They indicate that in this experimental anaemia, produced by vitamine A deficiency, blood regeneration occurs only with, and in proportion to, the addition of vitamine A. Nothing could appear more logical, since no anaemia can improve so long as the set of conditions responsible for the anaemia do not change. This experimental anaemia does not bear any relationship to pernicious anaemia, and, in fact, they propose such deficiency not as a sole, but rather as a cooperative factor in the etiology of the human disease.

Barker and Sprunt emphasized the importance, on general principles, of treating pernicious anaemia by liberal and well balanced diets. Many others have with no recognizable specific reason, advised special diets of various kinds. Mosenthal showed that forced feeding can restore a positive nitrogen balance. Gibson and Howard showed, in careful metabolic experiments, that more favorable nitrogen and especially iron balances may be established in pernicious anaemia when diets rich in food iron, and comparatively low in caloric and protein values are given, and urged the use of iron-rich and vitamine-adequate diets in the treatment of this disease. This was, in part, a clinical application of high food iron diets, which had been found by Whipple et al (1920-1925) so valuable in causing blood regeneration in experimental haemorrhagic anaemias. Elders, much convinced of the possibility that sprue and pernicious anaemia possess a common etiology, and equally convinced that sprue is a deficiency disease, suggested that pernicious anaemia might be found at least amenable to improvement by well chosen food. Minot and Murphy found it permissible to speculate "on the possible partial rôle that some nutritional excess or deficiency may play in the etiology of the disease." With a special diet rich in proteins of good biological value, particularly high in liver, low in fat and carbohydrate, and with vitamins well balanced, these investigators have already obtained remarkable therapeutic results, more constant and lasting than those obtained by any other form or forms of treatment. The published work of Minot and Murphy has brought the whole problem of nutrition in pernicious anaemia to a sharp focus of interest. Their results have suggested the possibility that dietary factors may actually play a rôle in the production of the disease. No studies of the pre-disease diets of patients have as yet appeared.

*The geographic distribution* It is recognized that the disease is commoner in Northern Europe, the British Isles, and North America than elsewhere, that it is uncommon in Brazil and China, and never occurs in a full-blooded negro. The writer in 1925 collected statistics from many countries, which, though never published, indicated that in those countries from which statistics were available the death rate per 100,000 population ran usually from 3 to 6. In the provinces of Canada, New Brunswick was "high" with 9.0 and British Columbia from 6 to 10 per 100,000 of population. Ontario showed a yearly incidence of from 14 to 15 per 100,000 of population, the deaths from pernicious anaemia actually constituting 1.28 to 1.31 per cent of the total deaths. The reality of this high rate in Ontario has been impressed on the writer during several tours of this province where it is not really uncommon to find from 4 to 7 cases in a private practice at one time. Ontario shows, as well, a high incidence in simple goitre and recently in studying 85 cases of pernicious anaemia at their homes in Ontario the writer noted the occurrence of simple goitre in 3 of the patients. Whether by further study a relationship between pernicious anaemia and the geological structure might be defined is uncertain but it is of interest to note that Montgomery in investigating the distribution of the disease in Western Canada found that areas of highest incidence were apparently those in which the drinking water contained highest concentrations of the alkaline earths. He observed in these cases that the individuals acquiring the disease were the Anglo-Saxon, life-long inhabitants, and never the more recently settled Scandinavian immigrants.

#### SIMILAR CLINICAL ANAEMIAS

Waugh, in his classification of anaemias would regard that of pernicious anaemia as the idiopathic member of a limited group designated as "hyperchromic haemomyelotoxic anaemias." This group includes the acute haemolytic anaemia of pregnancy, *dibothriocephalus* infections, some cases of gastric carcinoma and some cases of sprue. No doubt certain other exceptional anaemias might come under this heading as well.

The common expression, "pernicious blood-picture" is a loose unstandardised term, the meaning of which varies according to the views

of the person using it. It is sometimes erroneously used to describe a frankly aplastic anaemia in which the recognized evidences of abnormal blood destruction do not appear. The evidences of abnormal blood destruction, especially disturbance of the pigment metabolism is of primary importance. Adopting this as an excluding point, several haemolytic anaemias may be found whose haematological data as a whole suggest pernicious anaemia. Such are encountered in a few of each of the following conditions: carcinoma of the stomach, syphilis, pregnancy, *dibothriocephalus* infection, sprue, colonic cancer, *balantidium coli* infection, aleukaemic leukaemia, malignant metastases to the bone marrow, and as Minot as well as Meulengracht have pointed out, in a very occasional case of myxoedema. However, these instances, judged even by purely microscopic evidence, seldom fulfil the requirements of typical pernicious anaemia. The crucial test is the predominance of macrocytes, heavily staining, and exhibiting in at least 80 per cent of their number, definite ovality of outline. It is possible, therefore, by very vigorous microscopic standards to exclude most of these instances. All standards we possess are nevertheless very occasionally defeated by cancer of the stomach, sprue and fish-tapeworm infection. Needless to remark even such blood identities as these do not justify their designation as pernicious anaemia. But when, in addition to blood identity, there appear in such cases the additional features of glossitis, achlorhydria, and combined degeneration of the cord, escape from the dilemma is found by making a double diagnosis. Such a dilemma may actually be encountered in gastric and colonic cancer and in sprue.

There is little doubt that carcinoma of the stomach and perhaps of the colon may at times produce a macrocytic anaemia in which the macrocytes are circular rather than oval and exhibit a degree of achromia never seen in pernicious anaemia. It is equally true that sprue not infrequently produces a severe anaemia in which marked anisocytosis is a striking feature but which is not pernicious anaemia but merely the anaemia of sprue. Furthermore, a few cases of *dibothriocephalus* anaemia show such a striking identity with that of pernicious anaemia that distinction rests on associated signs or on the discovery of the worm. The etiological value of such resemblances is to demonstrate that various known con-

ditions can cause very similar anaemias, a fact which puts us on guard in interpreting experimental blood-pictures and which indicates, too, that a so-called "pernicious blood-picture" is not a strictly specific phenomenon

In instances where the whole Addisonian complex supervenes in a known disease, we are driven to choose between accidental occurrence or casual relationship. It is not impossible that sprue and gastric cancer possess at times a common meeting ground with pernicious anaemia, in the nature of a fundamental process which, once brought into being, is identical in its operation and consequences. Again, it is also not impossible that the presence of *dibothriocephalus latus* in the intestine sometimes brings the unknown fundamental process into operation.

#### A REVIEW OF EXPERIMENTAL FINDINGS

Since most of the experimental work on this disease has been dominated by the conception that it is caused by a blood-destroying agent absorbed from the gastro-intestinal tract, it is necessary to define the so-called "haemolytic theory" and to consider also the general problem of poisoning from the intestine.

*The requirements of any hypothetical toxin.* It is to be clearly understood that no definite proof of a toxin exists. The absence of *in vitro* haemolysis by patient's serum may be made congruous with a toxin theory by supposing that the toxin, wherever produced, is immediately adsorbed to the erythrocytes, or is removed from the circulation by the reticulo-endothelial system, the latter being thus rendered inimical to the red cells. Extracts of the spleen in the disease are not haemolytic. Really the chief reason for hypothesizing a toxin is that, in *dibothriocephalus* anaemia, the cause is supposed to be the autolysis products of the worm, operative through absorption by the intestine. This is not a very logical reason since no one has shown that the truly *haemolytic* products are absorbable from the human intestine.

If a toxin be hypothesized, then unity of toxin is suggested by the strikingly similar clinical and pathological pictures in all cases. Plurality of toxins finds its best argument in the occurrence of subacute degeneration of the cord temporarily without anaemia, and perhaps in the occurrence of splenomegaly in certain cases. The difference



between the so-called "haemolytic" and "myelotoxic" cases might better be called a difference in "activity," and would then depend on the dose of toxin delivered to the body

If a toxin *per se* causes this disease, by direct action on the tissues pathologically implicated, and without the necessary intermediary cooperation of any vital function, it must possess both haemotoxic and neurotoxic powers. To account for remissions the toxin must possess antigenic properties or be produced by a fluctuant mechanism, or both

Any toxin must be shown to be specifically active in the body. Its lack of haemolytic activity *in vitro* would not disqualify it

Any toxin to be seriously considered would have to produce: (1) a megaloblastic marrow reaction, (2) a characteristic blood picture, (3) nerve tissue degeneration without neuroglial increase, (4) remissions either by intermitting doses or on constant doses

No such toxin has yet been demonstrated

*Gastro intestinal toxæmia.* Although Hunter's own investigations of various intestinal poisons did not support this conception he clung to it for several reasons. The marked symptomatology of the digestive tract was one. A still more convincing one was his interpretation of the haemosiderin deposits. Having demonstrated this iron pigment in the liver in higher concentration than in the livers of other anaemias, and having accepted haemolysis as responsible, he assumed that the haemolysis took place largely within the portal area

Since 1885 the intestinal toxæmia theory has held its own with special investigators and particularly with the rank and file of general practitioners. It has many ramifications and although it merges with the trite and common idea of intestinal "auto-intoxication" so glibly accredited with all manner of ailments, any thesis so long sustained by some clinicians deserves serious consideration.

Intoxication from the bowel has received a very excellent general evaluation from Alvarez. The greatest objections to the idea are the tremendous number of poisons in the lumen of the gut and the lack of knowledge of their individual absorbability by the mucosa. Much investigation of individual poisons has led in almost no instance to any proof of their absorption in harmful amounts into the general circulation. The toxin of *B. botulinus* is perhaps an exception. Intoxication from high obstruction admits the element of a pathologi-

cal state of the mucosa. The absorptive faculties of this tissue in health would appear to be uniformly very selective ones. As a second barrier to the ingress of harmful substances stands the liver with its detoxicating functions. Any specific hypothesis of auto-intoxication from the intestine would require to show at the onset that the suspected substance could pass into the general circulation in a harmful state. The only alternative to this requirement would be a demonstration of increased absorption by the mucosa in pernicious anaemia. Such a theory has been advanced by Koessler et al as one of the fundamental changes in the disease. If this were successfully shown to be true, intestinal intoxication would at once assume greater seriousness.

The only actual work in connection with pernicious anaemia which might lend support to the theory of auto-intoxication was that of Iwao who reported that tyramine injections in guinea-pigs produced a severe anaemia of "pernicious type". Since tyramine can be formed from tyrosine by *B. coli*, and is therefore normally present in the bowel, this work looked promising, but Koessler and Harris failed to confirm it.

The gastro-intestinal mucosa itself either alone, or in association with abnormal states, has been viewed with suspicion. About a dozen cases have been reported in the literature in which pernicious anaemia was associated with chronic intestinal stenosis. Seyderhelm as well as Burns and Dixon noted improvement in cases of pernicious anaemia subjected to enterostomy, but only while the bowel remained open. Seyderhelm produced a "macrocytic" anaemia in dogs by stenosing the small intestine near the ileo-caecal valve. In such dogs, and in cases of pernicious anaemia, Seyderhelm has noted an encroachment on the ileum of the colonic flora. Hayden's case of clinical and haematological pernicious anaemia associated with malignant tumour of the gall-bladder and partial obstruction of the duodenum and colon, suggested to him the absorption of a toxin, and an analogy with the toxæmia of complete intestinal obstruction.

Apart from obstruction or any gross lesion involving the digestive tube, the mucosa itself has long been suspected. Berger and Tsuchiya in 1909 found at autopsy in the intestinal mucosa of 2 cases an ether-soluble substance ten times more haemolytic *in vitro* than a similar

extract from normal mucosa. On enteral or parenteral introduction into animals it was still more haemolytic than its control and produced an anaemia bearing some resemblance to that of pernicious anaemia. This work could not be confirmed by others. Dogs in whom a severe intestinal catarrh was artificially produced showed in their mucosa a lipoidal substance closely resembling in its action that found in the mucosa of pernicious anaemia. Cornell noted, during an attempt to implant *B. welchii* in the intestine of dogs, an initial severe diarrhoea accompanied by an evanescent mild anaemia with definite anisocytosis. Howard (1911) stressed this aspect of the study of a toxic lipoid from the intestinal mucosa. The question deserves further study. Briefly, while there is every reason to suspect the gastro-intestinal tract, there is absolutely no reason positively to incriminate it of giving rise by any means whatsoever to a poison responsible for the disease.

*The intestinal flora* Every organism that inhabits the lumen of the gut in pernicious anaemia has been suspected of causing the disease. The enterococcus is increased in the stools and lives higher in the duodenum than in health or other disease. This is true also of *B. coli*. *B. welchii* is increased in the stools but no work has been published to indicate whether or not it lives higher in the duodenum. *Streptococcus longus* has been reported abnormally present in the duodenum in a high percentage of cases. From all the investigations made, two facts are significant. A good case has not been made out against any organism and no exceptional one, specific to the disease, has been found.

*The B. welchii theory* *B. welchii* (*B. aerogenes capsulatus*, *B. perfringens*) is an anaerobic, Gram-positive, encapsulated bacillus which spores with difficulty on artificial media. When living cultures are injected into the ear vein of a rabbit and the rabbit then killed and incubated a so-called "foamy liver" develops. The organism has been divided into four groups by Simmonds on the basis of its power to liquefy gelatine. It was first identified by Welch in a case presenting gas in the tissue at autopsy. It was later shown, especially in the great war, to be a constant factor in the production of gas gangrene. Bull and Pritchett demonstrated a soluble exotoxin possessing distinct haemotoxic and lethal elements. This toxin is thermolabile and

has antigenic properties. The antitoxin from the horse or rabbit neutralizes *in vitro* the haemotoxic and lethal elements and cures the symptoms of an acute experimental infection in guinea-pigs, if promptly administered.

A possible relationship between this organism and pernicious anaemia was first suggested by Christian A. Herter in 1906. He found *B. welchii* or its spores numerically increased in the stools of this disease as compared with the stools from normal or other diseased conditions. Simonds later confirmed this finding. Although he was working at a time before the exotoxin was known, Herter felt that the stools showed altered chemical features due to this organism. He very tentatively suggested that *B. welchii* might be the cause of the disease, evidently meaning that in doing so it led a life confined to the lumen of the intestines, while its harmful growth products were absorbed into the circulation. His hypothesis therefore must be interpreted as a specific application of the intestinal intoxication idea, for he made no suggestion of tissue invasion by this organism.

Cornell (1924) showed that *B. welchii* caused a chronic infection when injected subcutaneously or intrasplenically into rabbits. This infection ran a course of several months and was characterised, among other symptoms, by an anaemia of varying intensity, whose constant feature was anisocytosis. This anisocytosis was due to a direct action of the exotoxin on the erythrocytes and occurred *in vitro* on washed cells. The smear picture bore no little resemblance to that of pernicious anaemia, but the macrocytes were characteristically circular rather than oval, the microcytes appeared like contracted rather than fragmented cells, and neither blood platelets nor leucocytes were depressed sufficiently.

Kahn and Torrey working at the same time on the effect of intravenous injection of the toxin in monkeys, obtained very similar blood pictures, but with higher colour indices and more leucocyte depression. Reid, Orr and Burleigh showed that a highly virulent strain of *B. welchii* would produce an infectious anaemia in rabbits whose acuteness or chronicity depended on the age of the culture used but that, in any case, anisocytosis was conspicuous and resembled quantitatively that of pernicious anaemia.

Moench, Kahn and Torrey in an analysis of the faecal flora in 35

cases of pernicious anaemia showed that *B. welchii* gives uniformly higher counts than normal, that of 26 different strains isolated 50 per cent conformed to Simond's Type I, but that none could be shown to be more haemolytic or pathogenic than *B. welchii* from normal persons' stools. They consider that if *B. welchii* is to be brought into etiological relationship with pernicious anaemia it must be because of its increased numbers and activity at a level of the tract higher than ordinarily, where absorption is more active. They support Seydewitz's observation of the invasion of the ileum by the colonic flora and consider this to be of importance.

Nye showed that an equal or even greater increase of *B. welchii* spores could be demonstrated in the faeces of cases of uncomplicated achlorhydria. He feels that the phenomenon depends on an alkaline condition of the proximal ileum and is therefore merely a consequence of achlorhydria and not an etiological factor in pernicious anaemia.

A bacterial study of the stools at Guy's Hospital does not seem to have confirmed the invariable presence of *B. welchii* in increased numbers (personal communication from Dr. Eyre).

There is no convincing evidence to support this hypothesis. The toxin has neurotoxic properties but the chronic infection in rabbits showed no combined system disease, no alterations in the gastric secretion, and no remissions. The toxin has never been shown capable of absorption from the intestine. In fact it is questionable if the organism living in the gut could produce a toxin comparable to that produced under very special culture conditions. It is probably cannot be regularly found in the internal organs after death and its presence might always be due to agonal invasion. In some animals this organism may be cultured from the liver during life and health. No agglutination or complement fixation by the serum on the organism or its toxin has been found, although both have been looked for. The blood picture produced by the chronic infection or by the continued injection of toxin, while definitely suggestive, is really not the blood picture of pernicious anaemia and may best be classified as a toxic, macrocytic, haemolytic anaemia. Finally *B. welchii* antitoxin has been repeatedly administered to patients without visible benefit.

*The streptococcus theory* Hunter (1909) made microphotographs of the glossitic lesions showing a long streptococcus in the subepithelial

layer of the tongue at those eroded areas where the mucosa was gone. From such lesions he claims to have obtained this organism in a highly virulent state in pure culture. To this organism he attributed largely the septic manifestations which so frequently accompany or antedate the true specific anaemia, but he never incriminated it as the cause of the latter. Haemolytic streptococci have been found in the gall-bladder in cases of cholecystitis associated with pernicious anaemia. Knott found, as did Hunter, large numbers of living *streptococcus pyogenes longus* in the gastric contents of patients and in increased numbers in the saliva. Ryle sets forth, as characteristic of a streptococcus fever, a rapidly progressive anaemia, a curiously smooth red desquamated tongue, both of which features are caused by a circulating cytolytic toxin. Newburg has reported a case of pernicious

TABLE 1  
*Streptococcus longus* in the duodenal contents

	NUMBER OF CASES	S LONGUS PRESENT	PERCENTAGE
Normal	4	0	11.5
Infective jaundice	8	0	
Various medical cases	14	3	
Pernicious anaemia	7	7	100.0
Subacute combined degeneration of the cord	4	4	

anaemia in which a haemolytic streptococcus was cultured from the blood. Hurst is the leading exponent of the streptococcus theory of the cause of the disease. Having first demonstrated that achlorhydria was as constant in pure cases of subacute degeneration of the cord as in pernicious anaemia, he made cultures of the duodenal contents during life on 4 patients with the former and 7 with the latter form of disease, and employed as controls 26 cases, either normal, or suffering from other conditions without achlorhydria. Table 1 gives his results.

No detailed description of the technique employed in this culture work has come to our notice, but accepting the results as stated to be bacteriologically beyond criticism, their interpretation is hazardous. Hurst concludes in part that the presence of *streptococcus longus* in the

duodenum is evidence of active infection of the intestine. This may be true, but does not mean necessarily any tissue invasion. He leans rather to the view that this organism by decomposing unaltered protein gives rise to haemotoxic and neurotoxic bodies which on absorption cause the disease. To make such a hypothesis convincing, the organism would need to be shown capable of forming such bodies, and these bodies would need to be capable of intestinal absorption. No records of this having been done appear. Experimentally the *streptococcus longus* has not been shown capable, by tissue infection, of producing an anaemia of the pernicious type. Hurst states, "In one of our patients an autogenous vaccine made from *S. longus* isolated from the socket of an infected tooth gave rise to a temporary aggravation of the sensation of pins and needles in the hands and feet each time it was injected." Cornell noted the same phenomenon when patients were injected with formalized or plain *B. welchii* toxin. Probably it is due to a non-specific protein reaction and of no etiological significance. Again, no serological reactions on pernicious anaemia in connection with streptococcus have been found and anti-streptococcus serum exerts no beneficial effect on patients with the disease. This latter fact has been amply attested to.

Recently Moench, Kahn and Torrey found streptococci very numerous in the stools of 33 cases of pernicious anaemia. The strains were of the normal intestinal types, no representatives of the haemolytic group being encountered.

*The B. coli theory.* Adams suggested in 1900 that in pernicious anaemia "we deal with subinfection by means of haemolytic intestinal bacteria of the colon group." A similar supposition played a part in this author's explanation of hepatic cirrhosis. It means that these special strains of *B. coli* invade the intestinal wall, enter the portal blood and then break down, somewhere in the body, liberating destructive endotoxins which are haemolytic and neurotoxic. Such a hypothesis defends itself in so far as it at once circumvents the difficulties inherent in an intestinal intoxication theory. It is plausible in that it specifies an organism abundantly present in the lumen of the gut. Moench, Kahn and Torrey were struck by the uniformly high counts for *B. coli* in the stools of pernicious anaemia patients, being much higher than for normal persons or people with other pathological con-

ditions Lowenberg recently showed in culturing the duodenal contents that *B coli* was present in 85 per cent of cases of pernicious anaemia and in only 35 per cent of cases of uncomplicated achlorhydria, whereas nothing like the same discrepancy occurred between the two same groups with regard to the finding of enterococci (90 and 75 per cent respectively) Routine cultures of pernicious anaemia organs at autopsy frequently shows *B coli* in the spleen and bone marrow Percy in cultures of organs made at laparotomy on spleens, gall-bladders, and appendices of nine cases of pernicious anaemia, found *streptococcus haemolyticus* in 7 cases, *B coli* in 5, *streptococcus viridans* in 4, and *staphylococcus albus* in 1 Experimentally, Nyfeldt, by injecting rabbits intravenously with either the whole autolysates or extracts of the autolysates of various intestinal bacteria, particularly *B coli*, was able to produce in 7 out of 15 animals the blood-picture and histological lesions of pernicious anaemia, while the remaining 8 developed a simple anaemia All these facts are very interesting, but more investigation is needed

#### OTHER INFECTIOUS THEORIES

Macora has reported the finding of typhoid bacilli at autopsy in the spleen and bone marrow Stanzoni has noted anaemia of "pernicious type" at the height of typhoid fever Kline has reported the finding of the proteus bacillus in the bone marrow, and the production of a haemolytic exotoxin from this organism has been reported by Ecker and Brittingham

Wood has found the *monilia psilosis* in the faeces of 15 cases of pernicious anaemia, while from 40 cases which were neither pernicious anaemia or sprue this yeast was not recovered Experimentally, by feeding this monilia to guinea pigs on normal diet, he produced a macrocytic anaemia with hepatic siderosis and extension of the red bone-marrow with normoblast increase Wood has been impressed, as has Elders, by the striking relationship between sprue and pernicious anaemia Musser has emphasized the common finding of free HCl in sprue Fontaine, in discussing Wood's work, stressed the common finding of a "secondary" anaemia in sprue, the different type and greater incidence of diarrhoea in sprue, and his own inability to find the monilia in cases of pernicious anaemia Nevertheless the work of



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Wood has found the *monilia psilosis* in the faeces of 15 cases of pernicious anaemia, while from 40 cases which were neither pernicious anaemia or sprue this yeast was not recovered Experimentally, by feeding this monilia to guinea pigs on normal diet, he produced a macrocytic anaemia with hepatic siderosis and extension of the red bone-marrow with normoblast increase Wood has been impressed, as has Elders, by the striking relationship between sprue and pernicious anaemia Musser has emphasized the common finding of free HCl in sprue Fontaine, in discussing Wood's work, stressed the common finding of a "secondary" anaemia in sprue, the different type and greater incidence of diarrhoea in sprue, and his own inability to find the monilia in cases of pernicious anaemia Nevertheless the work of

Wood is of great importance since he has demonstrated that, at least in the neighborhood of his clinic in North Carolina, many cases are seen in which either the diagnosis of pernicious anaemia or sprue is equally justifiable, even when glossitis, achlorhydria and combined degeneration are adopted as diagnostic points. The writer feels that two factors are to be taken into consideration in this confusion (1) The smear picture of uncomplicated sprue bears, especially in the presence of severe anaemia, a striking resemblance to the smear picture of pernicious anaemia (2) Sprue is, in some unknown manner, capable at times of setting in motion the fundamental bodily process which is operative in idiopathic pernicious anaemia, and bears to the Addisonian complex the same provocative relationship possessed by the fish-tapeworm infection. In other words, in a country where sprue is common, it may constitute the "releasing factor" of pernicious anaemia.

Broun et al (1926) in experimental work with the *monilia psilosis* could not produce a blood-picture approximating pernicious anaemia in man. By the use of an antigen prepared from monilia, some cases of pernicious anaemia showing monilia in the faeces were made to give positive complement fixation reactions, but so also did the sera of cases, other than pernicious anaemia, who harboured the monilia.

Logan found *Balantidium coli* in the faeces of a number of cases of pernicious anaemia, but does not feel either that all cases of balantidium have pernicious anaemia or that all cases of pernicious anaemia have balantidium. He suggests (1926) the importance of a study of the toxin production of humanized strains.

Meesen believed he had demonstrated spirochetes in the blood of pernicious anaemia but Determenn a few months later showed that what Meesen had considered motile spirillae were actually hemokones or "blood dust."

No evidence of a filterable virus has been reported.

#### MISCELLANEOUS THEORIES

The following hypotheses have never proved convincing—Sahli's Iron Theory, Allport's Sanguinin Theory, several endocrine theories, and many theories specifying individual substances such as blood phenols.

## THE VALIDITY OF EXPERIMENTAL BLOOD PICTURES

A large number and variety of agents can produce on parenteral injection blood pictures of a macrocytic character bearing more or less resemblance to that of pernicious anaemia—ricin, saponin, acetanilid, pyrocin, potassium-chlorate, pyrogallol acid, glycerine, nitro-benzol, trinitritoloul, toluodiamin, *B welchii* toxin, oleic acid, and various tissue extracts. Some of these may cause a marrow reaction of a megaloblastic type. This heterogeneous collection of agencies makes it clear that a macrocytic smear picture is not at all a specific phenomenon. Probably none of these pictures show the finer, and obviously necessary, features of that of pernicious anaemia. Exposure over long periods to radium and x-rays gives a similar, though aplastic picture. It is unlikely that any proposed agent will receive serious consideration as the etiological agent unless it can produce, in addition to anaemia, combined degeneration, glossitis and achylia. Moreover if such an agent could fulfil these requirements it would not be absolutely certain that it was identical with the toxin operative in the disease, pernicious (Addison's) anaemia.

## CONCLUSION

Pernicious anaemia appears to be a superstructure of blood system and nervous changes superimposed upon an unknown but characteristically fluctuant foundation. Of this foundation we know nothing, but conceive of achlorhydria as its constant and only obvious expression. It is not impossible that several different factors may bring the unknown fluctuant process into operation. It is further possible that this process depends chiefly upon idiosyncratic characters of the patient. The wide-spread tissue involvement found, and the peculiar mass of biochemical changes suggest that this fundamental process is a disturbance of metabolism.

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# THE EFFECTS OF COMPLETE AND OF PARTIAL REMOVAL OF THE LIVER

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## INTRODUCTION

A review of current medical literature reveals the fact that the liver, including the biliary tract, now occupies a very prominent position. It is indeed rare to find a number of any of the more important medical journals in which one or more articles having a direct or indirect bearing on the liver is not found. A little more than a decade ago, when I first began investigations dealing with various phases of activity of this organ, such a condition did not exist. At that time the discovery of the almost unbelievable physiologic significance of the ductless glands was too recent and researches on these hitherto little considered structures too alluring to allow much time for investigations on the seemingly better known organs. The clinician of the past has reduplicated the lack of interest of the physiologist in the liver. In general there have been clinically only three main points of interest in regard to the liver and each of these is a pathologic condition, namely (1) disease of the biliary tract, (2) jaundice, and (3) cirrhosis. It is probably significant that each of these conditions may usually be of some surgical importance.

While the active interest in the liver physiologically and clinically in the past has not been great, the organ has been of notable importance in a negative sense. Probably owing to the peculiar anatomic position of the liver, its complex physiologic relationships and obscure involvement in disease, definite facts regarding its function and relation to pathologic conditions have been difficult to obtain. Consequently in many instances, findings and observations which could not be considered as functions of any particular organ or tissue have been ascribed to the liver, mainly because it seemed impossible to prove such statements when applied to this organ. A similar statement could also be made concerning the clinical status of the organ, as is attested by the common diagnosis of biliousness, and the large number of supposed cholagogues. In many respects the liver has served as the wastebasket of the body into which have been dumped numerous manuscripts of conjecture concerning obscure physiologic and pathologic phenomena, and uncounted prescriptions.

However, the known facts concerning the physiology of the liver demand its acceptance as one of the most important organs in the body.

The liver occupies a unique and distinct position anatomically and physiologically. Its relatively large size, double blood supply and the elaboration of an external secretion and activities of a nature similar to the production of an internal secretion, all attest to its physiologic significance. Throughout both fetal and adult life the liver is the largest and most prominent organ in the body. One of its two sources of blood supply is conveyed to it under high pressure and the other under low pressure. The latter, to a considerable extent in fetal life, and wholly in adult life, drains the area responsible for the absorption of food and consequently may contain an abundance of products only partially prepared to enter the general circulation and to come into intimate contact with all the cells of the body. Its external secretion which in some respects is an excretion, is of great value in the digestion of one of the major foodstuffs. Its activity in regard to the exchange of constituents of the blood passing through it is of vital significance.

It would seem from the foregoing, therefore, that the liver is of the importance which its large size would indicate. In this regard it should be noted that the two largest masses of homogeneous tissue in the body, hepatic and voluntary muscle, have each recently been subjected to a renewal of interest and intensified investigation, whereby the old conceptions of their activity have been clarified and new conceptions have been promulgated. Such interest in the liver has been due to several factors, among which may be mentioned (1) development of technical methods for determining quantitatively the various constituents of the blood and urine, (2) the discovery of insulin with the stimulation of investigations of carbohydrate metabolism, a process in which the liver is intimately concerned, (3) the improvement of technical methods for studying the secretion of bile and its constituents, (4) important advances in regard to the physiology of the biliary tract, (5) development of tests of hepatic function, and (6) development of technical methods for removing the organ in the mammal.

It is difficult to overestimate the value of the recently developed accurate methods for determining quantitatively the various important constituents of the blood, tissues, and excretions. Without the development of these methods for which credit must chiefly be ascribed to the biochemist, many of the recent important advances in physi-

ology could not have been made. This applies with particular emphasis to the liver. The phases of hepatic activity concerning which we know the least are those for which quantitative methods have not yet been devised.

The discovery of insulin has stimulated an almost unprecedented amount of work on various phases of carbohydrate metabolism. These investigations have dealt with blood sugar, glycogen, hypoglycemia, and so forth, factors in which the liver is either directly or indirectly affected. However, much of this work has been barren in regard to depicting anything new concerning hepatic activity, although exceedingly valuable in regard to carbohydrate metabolism.

The studies of the secretion of bile still maintain an important place in physiology and the recent improved methods of obtaining this secretion free from infection and not modified by the activities of the gallbladder have done much to make observations on this phase of hepatic activity more trustworthy. Here again the development of biochemistry in devising methods for estimating the various constituents of bile has been of great value.

Until rather recently the biliary tract, including the gallbladder, has been mainly of concern to the surgeon. However, the discovery that the removal of the gallbladder is followed by definite changes in the remaining extrahepatic biliary tract, that this viscus greatly concentrates bile, that it prevents the development of jaundice for a long period after obstruction of the common bile duct, that it empties following the ingestion of certain foods, that the emptying is due to active contraction of its intrinsic musculature, that it is possible to visualize the gallbladder by means of a dye specifically excreted by the liver and concentrated in the gallbladder has been productive in stimulating interest in the biliary tract and liver.

The development of the so-called tests of function for estimating the function of the various organs has been of great value in correlating physiologic activities with clinical conditions and physiology with clinical medicine. While in attempting to develop tests of function for the liver much has been done that is of little or no value, some of the tests give promise of being of importance clinically.

Finally the development of methods for removing the liver of mammals surgically together with the employment of the chemical

and physical methods of quantitative determination of the changes occurring in the dehepatized animal has been responsible for procuring definite and quantitative data concerning the physiology of this great organ. It is my privilege to review briefly some of the results of the awakened interest in the liver in regard to its physiologic activity. That all such activity represents a permanent advance in our knowledge of the organ must not be too hastily accepted. An attempt will be made to emphasize the facts which appear to be of the most value to clinical medicine. In preparing this review I have drawn freely on my own previous publications and on those of my colleagues, both as regards review of previous work and new data.

#### METHODS OF INVESTIGATING THE FUNCTIONS OF THE LIVER

The present-day knowledge concerning the functions of the liver has been derived from many sources and is the accumulation of many methods of investigation. These various methods can be classified somewhat in the manner suggested by Carlson (24). In considering the physiologic significance of the liver and method of determining hepatic activity, it should be noted that anatomically and functionally the organ is composed of two groups of cells, the hepatic and the stellate. The functional activities of the two groups are different, although there may be some activities in which they are coordinated.

*Study of biliary secretion.* In earlier investigations, made at the time when the secretion of bile was the only known function of the organ, observation on the external secretion of the liver and its constituents was the only method of obtaining data on its functions. Investigations on the secretion of bile and the collection of the secretion of the liver are difficult because normally this secretion is poured into the duodenum. The difficulty is overcome by the employment of a biliary fistula. However, a possible source of error in studying bile secreted through a biliary fistula is in the gallbladder itself, which is present in most species of animals used for biliary fistula experiments. The concentrating action of the gallbladder is sufficient to decrease greatly the value of the investigations on biliary secretion with the organ intact. It is probable that certain of the diverse data on bile flow and bile concentration are due to the variable factor of gallbladder activity. Refinements in the technic of making biliary



fistulas, (Mann (119) and Rous and McMaster (192)), removal of the gallbladder, and greater care in the prevention of infection have greatly enhanced the value of this method in estimating hepatic function. Much of significance concerning the activities of the liver has been learned by a study of the bile fistula animal (Hooper and Whipple (82) and Rous (149)). It should be emphasized that this is only one function, and probably not the most important of the functions of the liver.

*Study of acute experiments* Various procedures have been carried out in acute experiments, that is, experiments in which the animal is maintained under anesthesia throughout the period of observation, for the purpose of obtaining evidence of the activities of the liver. The procedures have included the collection of bile, examinations for various constituents of the content of the blood going to the liver as compared with that coming from the liver, determination of the effect of the injection of various substances into the portal vein, and so forth. While valuable data have been secured in this manner in regard to some of the functions of the liver, the results obtained must be carefully considered before conclusions are drawn. The procedures have the objections which attend all acute experiments, effect of the necessary anesthetic or narcotic, loss of blood, variation in temperature, and so forth. The double blood supply of the liver, one of which is venous, makes it difficult to study the comparative constituents of the blood entering and leaving the organ. With reference to the method of studying the action of the liver by the effect produced by the injection of substances into the portal vein, it should be noted that in most instances the value of such experiments is greatly decreased because of a failure to determine whether the same results would be obtained by a similar injection into another vascular area, for example, the femoral artery (Koessler and Hanke (99)).

*Perfusion of the liver* The perfusion of an organ has been a popular method of investigating specific functions. It has been employed frequently in reference to the liver and many suggestive data have been thus obtained. The method has several serious objections which apply with particular force to the liver. It has proved almost impossible to devise a perfusing fluid sufficiently physiologic to maintain adequate circulation through any organ. Usually within a short time

after perfusion is begun the organ becomes edematous and circulation gradually ceases. It is particularly difficult to perfuse the liver, not only because it has two sources of blood supply in which normally there is a vast difference in the pressure maintained, but also because the hepatic cell appears to be affected so easily by changes in the fluid traversing it. While some facts of value have been obtained by this method of study of hepatic function, in many instances the results have been inconclusive (Macleod and Pearce (114))

*Chemical and histologic analysis of hepatic tissue* The chemical analysis of hepatic tissue has been of value not only in determining some of the important constituents of the organ but also in indicating changes in these constituents under various conditions. A study of the cytology of the liver has been of considerable value, particularly in regard to the storage and phagocytic function of the stellate cell and the great variation in activity of the hepatic cell (Mann (122))

*Studies of disease conditions of the liver* Careful studies of the liver in disease have yielded valuable suggestive data concerning its physiologic activity (Stadie and Van Slyke (209), and Chesney, Marshall and Rowntree (26)). However, such data should be interpreted carefully because of the difficulty of determining a normal condition from the results of study of a pathologic one.

*The effect of hepatic poisons* The discovery that certain poisons are more or less specific for the liver afforded another method of studying the organ experimentally. Several such poisons have been discovered, and much of value concerning their action on the liver in the production of various pathologic lesions have been noted, together with some facts concerning hepatic physiology. However, the same caution must be used in determining the value physiologically of such studies as in those dealing with hepatic disease (Williamson and Mann (230)).

*The Eck fistula animal* Numerous studies have been made on animals in which the portal blood had been diverted from the liver by an anastomosis of the portal vein and vena cava with a ligation of the former on the cephalic side of the stoma. Such studies have had two purposes: (1) determining the action of the liver in regard to the products absorbed from the alimentary tract, and (2) decreasing the function of the liver. The procedure has been of some value in the former, but in the latter it is questionable if the decrease in function

is sufficient in the average instance to make it of any value. The value of studies on the Eck fistula animal has probably been overestimated (Mann and Bollman (124))

*Extirpation of the liver* One of the oldest methods of attempting to determine the activity of an organ has been to study the effect of its removal. In this manner many facts of great value have been learned concerning various organs of the body. However, the defects of the method must be clearly recognized. Conclusions with regard to the function of an organ must be drawn cautiously if they are based on a study of the effect of its removal. The sudden loss of an organ may demonstrate conclusively that the organism can or cannot live without it, that certain physiologic processes are interfered with or stopped, that the functional activities of other organs are affected, and so forth. Such results may not indicate how the organ functions and it is always quite possible that many of the results following removal may be secondary and not directly related to the activity of the organ in question. However, many significant data have been revealed by a study of the effect of removal of the liver.

Since there are many methods of determining the facts concerning the functions of the liver and since the knowledge concerning such functions is incomplete, it seemed that the best method of presenting those most definitely proved would be a review of the results obtained with one method of approach. Accordingly, I shall review the results obtained by a study of the total and partial removal of the liver, placing special emphasis on the more crucial data that appertain to the functional significance of the organ and its relation to clinical medicine.

#### METHODS OF REMOVING THE LIVER

*Removal of the liver in the lower vertebrates* The total removal of the liver in the lower vertebrates is a fairly simple procedure. In these species there is a venous connection between the portal system and the systemic venous system, and the circle of Jacobson, which permits blood to return from the viscera to the heart without passing through the liver. Furthermore, the anatomic relation is such that the venous return from the lower extremities need not be injured by removal of the liver. The earlier experiments dealing with ablation

of the liver were performed, owing to the anatomic and surgical simplicity of the procedure, on the lower vertebrates, such as the goose, duck, frog, turtle and fish. It should be noted that in many instances the natural anastomosis between the portal and systemic venous systems is not sufficient to accomodate all the blood in the portal vein without producing some increased portal back pressure. This complicating factor is probably responsible for some of the contradictory data obtained by different investigators.

*Removal of the liver in mammals* The total removal of the liver of the mammal is much more difficult. There are two problems associated with the procedure which do not complicate the surgical removal of other organs. (1) maintenance of the circulation from the viscera and (2) maintenance of the circulation from the lower extremities. Since in the mammal all the blood draining the viscera flows through the liver, its removal in the normal animal results in portal obstruction, which always produces death. Normally most mammals do not have sufficient collateral circulation from the lower extremities to survive the sudden occlusion of the vena cava at the site where the liver encircles it. It is thus readily seen that the liver cannot be removed in the mammal unless some provision is made either for maintaining the portal circulation without its passing through the liver or eliminating the abdominal viscera. It is also impossible to remove all the liver without injuring the vena cava at the site where the hepatic veins empty into it. Some provision must thus also be made for maintaining the venous return from the portion of the body caudad to the liver.

Many different methods of removing the liver have been devised. In most of these the organ is removed only functionally, that is, the blood supply either to the whole body caudad to the liver or to the organ itself is cut off by ligature, but the organ is left in situ. In other methods the organ is actually partially or wholly removed from the body. Usually the abdominal viscera are also removed. However, with some methods provision is made for maintaining the portal circulation and the venous return from the lower extremities. In many experiments the liver is injured, that is, removed chemically by the more or less specific hepatic poisons.

The first experiments on removal of the liver in the mammal con-

sisted in ligation of all the blood vessels, abdominal aorta, portal vein, and inferior vena cava below the diaphragm. This procedure not only cut off the blood supply to the liver, but also to all the other viscera and to the lower extremities. Only the head and thorax had adequate circulation, this has given rise to the term, "head-thorax preparation." The method, with slight modifications, has been used by several investigators and some observations of considerable value have been made. On the whole, the experiment has not been altogether satisfactory so far as obtaining data on the functions of the liver is concerned, and there are many objections to it. The experiment is necessarily complicated by an anesthetic throughout the entire period of observation. Many other organs are removed as effectively as the liver. Less than half the body is under observation. The blood volume and blood pressure are markedly altered. It would seem that conclusions on the function of the liver based on such experiments should be drawn cautiously. A less valuable method than the foregoing is ligating the base of the liver, probably obstructing both the portal vein and the vena cava. This not only stops the circulation of the viscera and lower extremities, but allows blood to accumulate in these areas.

One of the most common methods of functional removal of the liver is by means of an Eck fistula, and at the same time, or later, ligation of the hepatic artery. This leaves the organ in the peritoneal cavity but removes the liver functionally by shutting off its blood supply. It is apparent that there are certain serious objections to this method. Undoubtedly certain vessels from the diaphragm enter the liver, therefore a very small portion of the organ would have a blood supply. This, however, is probably of little practical significance, since the amount of tissue thus supplied would be small. The main objection to this method is that the hepatic veins still drain into the vena cava and the hepatic tissue is still in the peritoneal cavity. The tissue thus cut off from its blood supply in the peritoneal cavity quickly undergoes autolysis. The tissue gives up its glycogen and autolysis soon makes the organ almost unrecognizable. The products of such an autolyzing liver are extremely toxic (Mann and Magath (131), Mason and Davidson (142)) and easily gain entrance into the circulation through the open hepatic veins and by absorption from the

peritoneal cavity This not only shortens the animal's life, but modifies the clinical condition as well as the constituents of the blood, and there is a possibility of attributing to hepatic function something which is due only to destroyed hepatic tissue When this method is employed, the animals usually live less than half as long as when the organ is totally removed

In the first experiments in which the liver was actually removed from the body, all the viscera drained by the portal vein were also removed This has been termed the "evisceration method" There are two objections to this method Since so many other organs are removed, the results obtained must be carefully analyzed before they can be attributed solely to loss of the liver The most serious objection however, is the fact that the liver encompasses the vena cava closely and, in order to remove all of its tissue, the vein is injured, and the venous return from the lower extremities accordingly obstructed This method appears to be of but little value

A much more valuable method of removing the liver consists in performing an Eck fistula and later removing the organ lobe by lobe Here again the intimate relation of the vena cava and the liver makes it impossible to remove all of the liver without injuring the vena cava It is necessary to leave a minimum of 10 per cent of the tissue in order to leave the vena cava intact, since by removing all of it, the vena cava will be injured, and circulatory destruction in both the viscera drained by the portal circulation and the lower extremities will follow, while if some of the tissue is left without adequate blood supply, it undergoes autolysis and causes complicating toxemia

A critical review of the methods of removing the liver explains, in many respects, the cause for the contradictory statements with regard to hepatic function The various methods of removing the organ are complicated by so many factors, that varied results were obtained by different investigators, and on the other hand, many of the results attributed to loss of hepatic function, were due to these complicating factors Among the complicating factors in the various methods, the following should be emphasized (1) often portal obstruction occurs, (2) the venous return from the extremities is obstructed or impaired, (3) only a small portion of the body is left intact, (4) other organs besides the liver are removed, and (5) hepatic tissue without blood

supply is left in the body so that autolytic liver products can enter the circulation. All of these factors contribute their part to produce the diverse results, confound the investigator, and make an analysis of the data with regard to hepatic function hazardous.

A method of total removal of the liver surgically in the dog was devised by Mann (118). With the realization that the successful removal of the liver in the dog was dependent on a solution of the two circulatory problems involved—that of maintaining the circulation from the lower extremities, and that of maintaining the venous return from the viscera, a method was evolved which forced the development of collateral circulation through other channels than the vena cava sufficient to maintain the venous return from the viscera and caudad half of the body.

The essential steps in the method are (1) performing a reverse Eck fistula, that is, making a lateral anastomosis of the portal vein and vena cava, and ligating the latter on the cephalic side of the stoma, (2) after waiting a sufficient time for collateral circulation to develop, ligating the portal vein, and (3) at a final operation removing all the liver. The basis for these procedures resides in the facts that (1) following the reverse Eck fistula collateral circulation usually develops in the dog, and (2) when the vena cava and portal vein need not be considered, the liver can be removed in a mass. Briefly the various procedures for the total removal of the liver in the dog are as follows.

The first operation is a reverse Eck fistula. While many methods for anastomosing the portal vein and vena cava have been described, the modification of the cutting suture method (Fischler and Schroder (52)) has been used to great advantage. Only the essentials of this method will be given as a detailed description has been made by Fishback (46).

A loose linen ligature is placed around the vena cava between the entrance of the lumbo-adrenal veins and the hepatic veins, care being taken to place it as close to the latter as the encompassing liver will permit. The vena cava is exposed from the point at which the ligature was passed caudally to the entrance of the renal veins. It has been found that collateral circulation develops better when the stoma is made in the vena cava as caudally as possible. Furthermore, this places the site of operation for the anastomosis of the blood-vessels as

far as possible from the site of operation at the subsequent removal of the liver. The portal vein is exposed for a distance equal to, and exactly opposite, the length of vena cava located. The adventitia is dissected away from the portal vein on the side next to the vena cava. A stay suture of fine silk is passed through the walls of both veins at the extreme ends of the portion of freed portal vein. A continuous suture is then employed to approximate the vein between the two stay sutures, using the needle on the caudal side. This is the posterior suture line of the anastomosis. A long, fine needle carrying a strong silk suture, termed the cutting suture, is then passed into the portal vein from below up and parallel with the previously placed suture line and within the limits of each end of this line. The cutting suture is then carried across and passed in the opposite direction in the vena cava. The points of entrance and emergence of the suture in each vein should be the same. The area of each vein included in the cutting suture is then buried by another continuous suture by using one of the needles of the stay suture which is now on the cephalic side. Care must be taken to close the upper angle carefully and not to catch the cutting suture with the continuous suture. The latter suture is not tied, but left as a loose mattress suture around the emerging ends of the cutting suture. Thus, by pulling back and forth on the cutting suture, the walls of both veins are cut through between the two rows of continuous sutures. The loose mattress suture is tied to the remaining end of the lower stay suture, thus closing the hole left by the withdrawal of the cutting suture. The ligature around the vena cava is then tied. The ligature is on the cephalic side of the anastomosis. This method of anastomosing the vein has proved satisfactory, although it is sometimes unsuccessful if the portal vein is small.

At first, after the reverse Eck fistula has been made, the pressure is increased in both the vena cava below the ligation and the portal system, and a considerable portion of the blood from the lower extremities passes through the liver. However, the capillaries of the liver appear to offer more resistance to the flow of blood than is necessary for the development of collateral circulation through the azygos and internal mammary veins, consequently most of the blood soon passes by way of the later channels. From two to four weeks after the first operation, the second operation can be performed, although



if necessary it can be postponed for several months. The second operation consists in ligating the portal vein at the usual site in performing an Eck fistula. This causes all the blood from the viscera and hind limbs to return to the heart by way of the collateral circulation. If, as often occurs, collateral vessels fail to develop sufficiently, as is recognized by congestion of the intestines after ligation of the portal vein, the occlusion of the portal vein is carried out in two stages. In such cases the vein is only partially occluded by passing a suture of fine silk through the center and ligating one side. At a later operation, the portal vein is entirely occluded. In certain animals collateral circulation is not developed sufficiently to allow the portal vein to be occluded safely. Practically all operative failures have been due to this lack of development of collateral circulation. The third and final operation consists in total removal of the organ. Owing to the fact that pulling on the diaphragm usually inhibits respiration, and also that the liver has a very definite mechanical function in offering resistance to the diaphragm, it was found best to use intratracheal insufflation during the final operation. With proper teamwork the removal of the liver can be quickly and easily accomplished. The gastrohepatic ligament with the contained structures is first sectioned between clamps, likewise the vena cava is clamped and sectioned on the cephalic side of the previously placed ligature. The whole organ can then be pulled out of the abdomen and the vena cava clamped and sectioned at its point of entrance into the diaphragm. All vessels must be securely ligated. It has also been found best to transfix the ligature on the vena cava at the point at which it passes through the diaphragm with a suture. After the various necessary procedures have been worked out the final operation can be performed so that the total length of time from beginning the anesthetic until its withdrawal rarely exceeds half an hour. If too many adhesions have not developed, very little blood need be lost. In order to decrease the time the animal is under the anesthetic, the abdominal wound is closed with large, heavy sutures of nonabsorbable material through the entire abdominal wall except the skin. The skin is closed with a deep, tight suture of linen. Such closure can be accomplished quickly and aids in hemostasis. There are few failures with the third operation. It should be emphasized that the final operation can, with proper

cooperation, be performed quickly. Light ether anesthesia is given. The liver is entirely removed without affecting in any way either the portal circulation or the venous return from the extremities. The animal is placed in a warming cage immediately after operation. Usually it is capable of walking around and in most respects appears normal in less than an hour after withdrawal of the anesthetic.

While the method of removing the liver described (Mann (118)) gives excellent and definite results, it is open to two objections. It requires three operations and it involves shunting the portal blood from the liver. In regard to the first objection it must be further considered that in a certain percentage of animals collateral circulation fails to develop and thus the total occlusion of the portal vein is prevented. In regard to the second objection, it is legitimate to question whether the injury to the liver following the diversion of the portal circulation might not be the cause of some of the results noted after total removal of the organ. There are many considerations which argue against the idea that injury to the liver due to loss of the portal circulation in any way complicates the effect of subsequent hepatectomy. Chief of these is the fact that total removal of the liver always produces the same result, whether the portal vein has been ligated four days or a year and a half previous to hepatectomy. However, in order to overcome both of these objections, other methods of removal were developed. It should be emphasized that in order to keep from changing the flow of blood through the portal vein before the final experiment, it is necessary to remove all the viscera drained by the portal vein. Such a procedure eliminates other organs besides the liver, and before the results of the experiments can be attributed to a loss of this organ, it is necessary to check these with experiments in which only the liver has been removed.

Four methods of removing all the intra-abdominal organs have been described. Since the main problems complicating removal of the liver are associated with the circulation of the extremities and the abdominal viscera, these must receive first consideration. The complicating results associated with the portal circulation are due to stasis, and can always be obviated by removal of all organs draining into the portal circulation. The circulation from the lower extremities can be maintained by forcing collateral circulation or taking advantage

of that already present The simplest method is to ligate the inferior vena cava just caudad to the entrance of the hepatic veins (Mann (121), Rich (186)) After a short time, when the collateral circulation has been developed, all the intra-abdominal viscera can be removed The objection to this method is that only about a third of the dogs will survive sudden occlusion of the vena cava It is possible to cause collateral venous return from the lower extremities by either one of two procedures which are more often successful than complete occlusion of the vena cava One of these is the performance of a reverse Eck fistula, and the other partial occlusion of the vena cava instead of complete (Mann (121)) Each of these methods is superior to the sudden ligation of the vena cava However, in each instance preliminary operation is necessary The following method has been found to be the simplest of removing all the intra-abdominal organs The success of the method depends on the fact that in the normal animal there is sufficient collateral circulation to return all the blood drained into the vena cava, caudad to the entrance of the hepatic veins, except that returning from the kidneys Under ether anesthesia, a long median-line incision is made and both kidneys removed quickly In performing the nephrectomy the arteries are clamped before the veins This prevents the loss of blood by congestion of the organs Then, starting at the celiac axis, all the arteries going to the intra-abdominal viscera are double clamped, sectioned and the central ends ligated Care is taken not to clamp or injure any of the veins until the arteries are ligated and thus much blood is saved After the arteries have been ligated the root of the mesentery is clamped, sectioned and the veins ligated The liver is then removed in the manner described for total removal of the organ Finally the esophagus and the rectum are sectioned and the proximal and distal ends respectively occluded The operative procedures can be quickly performed with but little loss of blood After the abdominal wound has been repaired the animal recovers quickly from the anesthetic and the operation, and it can be maintained in a normal-appearing condition for from fifteen to eighteen hours by means of proper postoperative treatment In general the condition of such animals appears to be similar to the condition of those in which the liver and kidneys have been removed They are excellent subjects for preliminary observations which can later be checked on totally dehepatized animals

## THE EFFECT OF TOTAL REMOVAL OF THE LIVER

*Course of events.* A characteristic syndrome was not observed in re-hepated animal by earlier investigators on the effect of total removal of the liver. Their failure to observe the development of a definite group of symptoms is easily understood. In most of the investigations, particularly those in which a mammal was employed, the animal was maintained under an anesthetic or narcotic so that symptoms could not be observed. Practically all the experiments were complicated by marked derangement of the circulation. In most investigations the experiments were performed in order to obtain definite data with regard to a particular fact concerning the liver, and general observations were not made. In the more complete investigations some species of the lower vertebrates were usually employed, as the goose or duck, in which the symptoms following removal of the liver are not so definite or marked as in the dog.

However, some of the characteristic symptoms of the dehepated animal had been observed. Minkowski (157) observed convulsions and coma in some of his goats after extirpation of the liver. Kauch (96) particularly emphasized the occurrence of convulsions in his dehepated geese. Hann, Marsen, Nenli and Pavlov (74) noted muscular twitchings, convulsions and coma in dogs in which an Ecd. fistula had been made and the hepatic artery ligated. Doyon, Gautier, and Policard (36) record the development of typical convulsions in frogs following removal of the liver. Whipple and Hooper (226) observed muscular twitchings in dogs with Ecd. fistula and ligation of the hepatic artery. Matthews and Miller (144) report that animals in which the hepatic artery is ligated some weeks after an Ecd. fistula had been made became comatose eight to twelve hours after ligation. Erdlyi (41) and Bargerold (22) have described convulsions and coma in Ecd. fistula animals that have been fasted and given phlorizin. Fischer (59) has noted the same phenomena.

Perroncito (175), owing to his method of removing the liver, was able to study the dehepated animal following recovery from the anesthetic, and immediate effects of the operation. His description of the symptoms which develop in the dehepated animal is complete and accurate and constitutes what is probably the first record of the well-known hypoglycemic condition due to removal of the liver,

of that already present The simplest method is to ligate the inferior vena cava just caudad to the entrance of the hepatic veins (Mann (121), Rich (186)) After a short time, when the collateral circulation has been developed, all the intra-abdominal viscera can be removed The objection to this method is that only about a third of the dogs will survive sudden occlusion of the vena cava It is possible to cause collateral venous return from the lower extremities by either one of two procedures which are more often successful than complete occlusion of the vena cava One of these is the performance of a reverse Eck fistula, and the other partial occlusion of the vena cava instead of complete (Mann (121)) Each of these methods is superior to the sudden ligation of the vena cava However, in each instance preliminary operation is necessary The following method has been found to be the simplest of removing all the intra-abdominal organs The success of the method depends on the fact that in the normal animal there is sufficient collateral circulation to return all the blood drained into the vena cava, caudad to the entrance of the hepatic veins, except that returning from the kidneys Under ether anesthesia, a long median-line incision is made and both kidneys removed quickly In performing the nephrectomy the arteries are clamped before the veins This prevents the loss of blood by congestion of the organs Then, starting at the celiac axis, all the arteries going to the intra-abdominal viscera are double clamped, sectioned and the central ends ligated Care is taken not to clamp or injure any of the veins until the arteries are ligated and thus much blood is saved After the arteries have been ligated the root of the mesentery is clamped, sectioned and the veins ligated The liver is then removed in the manner described for total removal of the organ Finally the esophagus and the rectum are sectioned and the proximal and distal ends respectively occluded The operative procedures can be quickly performed with but little loss of blood After the abdominal wound has been repaired the animal recovers quickly from the anesthetic and the operation, and it can be maintained in a normal-appearing condition for from fifteen to eighteen hours by means of proper postoperative treatment In general the condition of such animals appears to be similar to the condition of those in which the liver and kidneys have been removed They are excellent subjects for preliminary observations which can later be checked on totally dehepatized animals

of the dehepatized dog In general it seems to be practically normal while the animal is active When the first symptom develops the blood pressure may increase or decrease slightly, but does not necessarily change greatly It is definitely subnormal before death The pulse rate always increases immediately after removal of the liver and may remain about twice the normal rate until the animal becomes moribund The heart continues to beat for a long time after breathing has ceased Respiration undergoes certain changes following operation, varying with the condition of the animal Immediately after operation, and usually during the period the animal appears normal, the respiration is normal or slightly increased in rate When the animal is in coma, the Cheyne-Stokes type of respiration may be noted The temperature usually continues normal until the animal becomes flaccid, although just previous to the development of muscular weakness, it may rise slightly higher than it was before operation It may become subnormal before death Most of the animals secrete practically a normal amount of urine before symptoms develop, but occasionally some may be anuric throughout the postoperative period

Observations on the urine excreted by the dehepatized animal and analysis of the blood for the various important blood constituents, such as the nitrogen and sugar, demonstrated that certain changes invariably occurred after total removal of the liver These were (1) progressive decrease in sugar, (2) the appearance and progressive increase of a pigment, and (3) the progressive increase in uric acid The characteristic changes noted in the urine were (1) appearance of a heavy flocculent precipitate, and (2) appearance of a yellow pigment

*The blood sugar level and condition of hypoglycemia* The first experiments on the effect of exclusion of the liver on blood sugar seem to have been made by Bock and Hoffman (11) They excluded the liver from rabbits by ligating the abdominal aorta, portal vein, and inferior vena cava between the entrance of the renal and the hepatic veins Specimens of blood were obtained from the heart by passing an obturator through the inferior vena cava Animals thus operated on lived from two to fifty minutes The blood sugar decreased, and no sugar could be found in the blood of animals living as long as forty-four minutes These experiments have been criticized severely by subsequent investigators because the circulation is so greatly damaged

by the procedure Minkowski (157), in his classical research on the effect of removal of the liver in geese, noted a decrease in blood sugar. Seegen (204) excluded the liver in dogs by ligation of the aorta and vena cava above the diaphragm. The animals lived from twenty to seventy minutes. Marked reduction in the blood sugar was observed. Schenck (197) ligated the base of the liver, probably obstructing both the portal vein and the vena cava. A decrease in blood sugar was noted. Kaufmann (95) repeated Seegen's experiments, that is, he ligated the aorta and inferior vena cava above the diaphragm in dogs, and observed a rapid diminution of sugar in the blood. His animals lived about an hour. Kausch (96) repeated Minkowski's work on geese and corroborated his findings with regard to a decrease in blood sugar after removal of the liver. Macleod and Pearce (115) restricted the circulation in dogs to the anterior portion of the body and obtained a rapid reduction in blood sugar. Pavy and Siau (171) performed experiments on cats and dogs. In the former, all the viscera were removed except the liver, in the latter the liver and other organs also were removed. The blood sugar dropped progressively, but was never wholly depleted. Falta and Priestly (43) noted that the blood sugar declined in a head thorax preparation. Collens, Shelling and Byron (27) showed that exclusion of the arterial supply to the liver by ligation of the hepatic artery and its collaterals results in death with hypoglycemic convulsions.

The investigations of the effect of the removal or the exclusion of the liver on blood sugar, therefore, show that a reduction of blood sugar was obtained in each instance. Most investigators have attributed little significance to this fact. The liver was not removed surgically from any of the animals except the goose. The different methods of exclusion entailed a great alteration in the circulation, and except in those experiments in which the circulation was restricted to the anterior part of the body, great loss of blood must have occurred from congestion. The method of experimentation and length of life after operation, with the exception of experiments with geese, precluded any correlation between the reduction of blood sugar and the development of symptoms. In this connection it should be noted that hypoglycemia has been produced by some of the hepatic poisons. Frank and Isaac (63) made blood sugar determinations on rabbits

that had been poisoned by large doses of phosphorus and found a terminal hypoglycemia. Williamson and Mann (230) obtained but a small percentage of instances of hypoglycemia in dogs after the administration of chloroform and phosphorus. Underhill (216), MacAdam (111) and Bodansky (12) all noted hypoglycemia following the administration of hydrazin sulphate. Izume and Lewis (86) investigated the hypoglycemia following hydrazin administration and suggest that the primary cause is a failure of normal glycogenesis, the transformation of non-carbohydrate material to glucose, as a result of which the supply of glucose available is diminished because of the hepatic injury produced by the hydrazin.

The first experiments in which there was a correlation between the decrease in blood sugar and the development of symptoms were performed on the dog, (Mann and Magath (128)). It was observed that there was always a decrease in blood sugar after total removal of the liver. Of greater interest, however, was the fact that the concentration of sugar in the blood exactly paralleled the clinical condition. The blood sugar level before removal of the liver was usually slightly lower than the average for normal dogs. This is attributed to the fact that the portal blood supply of the liver had been deflected, as the average blood sugar of dogs with true Eck fistulas usually is slightly below the average for normal dogs. The anesthesia and operative procedure of hepatectomy do not cause the hyperglycemia which is usually noted after anesthesia and operative procedures on normal dogs. The blood sugar concentration immediately after hepatectomy was usually the same or less than that preceding operation, and rarely slightly higher, it decreased during the period the animal appeared normal. The level of blood sugar at which the first symptoms developed was usually quite definite and coordinate in the different animals. The actual figures depended on the method of determining blood sugar. In most of the dogs the blood sugar was 0.04 per cent. In some instances, the first symptoms were noted when the blood sugar was 0.05 per cent, and also when it was 0.03 per cent. The blood sugar decreased quite rapidly after the onset of convulsions, and at the time of death was usually not in excess of 0.03 per cent. This direct relationship of blood sugar and the development of symptoms and death was so constant that the amount could be estimated



correctly after a clinical examination of the animal's condition when it showed symptoms

*The effect of the intravenous injection of glucose* Although several investigators had observed the decrease in blood sugar following the loss of the liver, its significance was not appreciated owing to the methods of removing the organ which prevented clinical observations. Only after it was possible to study the development in the normal-appearing dehepatized animal of a characteristic group of symptoms leading to a moribund condition associated with a progressive decreasing blood sugar level, was it deemed possible that a certain concentration of sugar in the blood was necessary to life. However, the constancy of the decrease in the blood sugar in the dehepatized animal and the exact coincidence of the characteristic symptoms, led Mann and Magath (129) to investigate the effect of the administration of glucose on animals in which the liver had been removed. This was the beginning of the specific glucose therapy in the condition of hypoglycemia.

The effect of the intravenous injection of glucose on an animal dying from removal of the liver is one of the most remarkable of physiologic phenomena. The animal, comatose and perfectly flaccid, apparently unable to contract any muscles except those of respiration, is restored immediately to a seemingly normal condition by the injection of from 0.25 to 0.5 gram of glucose for each kilogram of body weight. Such apparently moribund animals will stand in thirty seconds after the injection of glucose, they will walk, respond to call, wag their tails, drink water, and so forth, in less than one minute from the time they had seemed dying. If convulsions are allowed to develop, which are followed quickly by death if untreated, the results are even more striking. The convulsions cease immediately, consciousness returns, and in a minute or two the animal walks around normally. Restoration to normal is usually possible by the injection of glucose at any stage of the moribund hypoglycemic condition until the heart has actually stopped. Animals have been restored after the cessation of respiration by maintaining artificial respiration until glucose could be injected.

Immediately after the injection of glucose, the blood sugar reaches a high level, at first it falls quickly, then more slowly. As the level

again becomes low, the typical symptoms reappear. The time at which this occurs after injection depends on many factors. Some of these are, the amount of glucose injected, whether the animal is active or quiet, and whether or not it is kept warm. Restoration from the comatose condition can be repeated many times by the injection of glucose. In each instance, the clinical condition exactly coincides with the blood sugar level. Finally, however, usually after many restorations, it may be noted that the same amount of glucose does not maintain the animal in a normal condition for so long a time, and the characteristic symptoms develop at a higher blood sugar level. It becomes restless and usually vomits. Its nose is characteristically placed against the cage door and it breathes with considerable energy, although dyspnea and air hunger do not seem to be the cause. The animal becomes ataxic and apparently loses both the sense of sight and hearing because objects are not avoided in walking and no response to sounds is elicited. Coma develops, which may persist for several hours. When death occurs, it is usually sudden and quiet. Anuria usually precedes this group of symptoms. The administration of glucose in no way modifies the second condition, although the glucose is necessary to prevent death from hypoglycemia.

Since glucose produced such a remarkable restorative effect on the hypoglycemic animal, it was desirable to determine if its continuous administration beginning immediately after removal of the liver would prevent the development of hypoglycemia. Accordingly, in some experiments before the blood sugar had decreased to a low level and before symptoms occurred, glucose was injected slowly and at a uniform rate. In this manner the blood sugar level was kept normal or slightly above normal. The first group of symptoms never developed in animals thus treated, but after eighteen to thirty hours, the second group developed and the animals died.

It was found that the administration of glucose, in any manner, so that it actually enters the circulation and maintains the blood sugar would also prevent the development of the characteristic symptoms and greatly prolong the animal's life. For instance, the continuous intravenous injection of glucose, its administration by mouth, by jejunostomy or by rectum, or its injection intraperitoneally or subcutaneously, all would prevent hypoglycemia and maintain life.

However, the administration of glucose by means of the gastrointestinal tract is complicated by a variation in the rate of absorption and also by the formation of gas, due to the action of bacteria. The intraperitoneal and subcutaneous rate of administration are not good because of changes in the rate of absorption. The best method has been either continuous intravenous injection of a glucose solution of low concentration, or the intravenous injection of a definite amount for each kilogram of body weight of a high concentration at definite intervals.

The intravenous injection of glucose will always restore to normal the dehepatized animal in the characteristic condition associated with hypoglycemia. A sufficient number of experiments have been carried out so that one may state definitely that it never fails. Furthermore, the administration of glucose to the dehepatized animal in sufficient amounts to maintain the blood sugar at the normal level always prevents the development of the characteristic group of symptoms.

It has been found that glucose is specific for restoring the hypoglycemic dehepatized animal to normal. A wide variety of substances which would seem to give some promise of a related action, were tested in the same manner and in amounts which seemed to correspond to the amount of glucose necessary to restore the dehepatized animal to normal. The substances tested and found not to have a restorative action were saccharose, lactose, levulose, inulin, sodium chloride, sodium sulphate, sodium carbonate, sodium bicarbonate, ethyl alcohol, glycerol, lactic acid (both racemic and d-lactic), acetic acid, hydrochloric acid, pyruvic acid, epinephrin, pituitary extract, and glycocoll. It should be noted that the negative results obtained by this variety of substances definitely prove that the symptoms associated with the hypoglycemia were not due to acidosis or alkalosis, and that the beneficial action of glucose is not due to an osmotic action.

Only five substances other than glucose were found to have a beneficial action when injected into the moribund animal with a low blood-sugar level following removal of the liver. These are maltose, mannose, dextrin, galactose and glycogen. The action of maltose is somewhat cumulative. When it is first injected into an animal with the characteristic symptoms following hepatectomy, the recovery is slow but complete. Ten minutes may elapse between the time

of the injection and the time the animal walks, whereas when glucose is injected, recovery is usually complete in from one to four minutes. When the animal becomes moribund again and maltose is again injected, the recovery is much faster than after the first injection. Mannose produces a response similar to maltose. Dextrin produces a definite but slight beneficial action. The animal will probably regain consciousness and muscle tone but will not be able to stand when dextrin is injected. The beneficial action of galactose is so slight and transient that it would scarcely be noted unless the animal were under the strictest observation. The response to the injection of glycogen is fairly rapid, and in most respects similar to that of glucose. The blood-sugar curve following the injection of glycogen is practically the same as though glucose had been injected. While it has not been determined definitely why these few substances are beneficial in the restoration of hepatectomized animals to normal, it should be noted that in most instances it is possible they are converted into glucose in the blood stream. The transformation into glucose would also explain the beneficial effect of maltose on hepatectomized dogs, and the release of excess maltase in the blood after the first injection explains the better and more prompt effect of the second. It is also possible that mannose may be changed into glucose in the blood stream. The beneficial effect of dextrin and galactose may be explained on the basis that they contain maltose and glucose as impurities. Thus far it has not been possible to obtain a pure specimen of dextrin.

While there have been individual variations in the reaction of the hepatectomized animal to various amounts of glucose, in general the quantitative relationship has been constant. The smallest amount of glucose which will produce a definite beneficial action in the moribund hepatectomized hypoglycemic dog is 0.125 gram for each kilogram of body weight. Smaller amounts than this usually do not produce noticeable effects or only questionable effects. One-eighth gram of glucose for each kilogram of body weight restores the animal to consciousness and enables it to stand, but not to regain its normal strength, and in a short time, from fifteen to thirty minutes, the comatose condition returns. When 0.25 gram of glucose for each kilogram of body weight is injected, the recovery is prompt and complete.

The amount of glucose necessary to keep the hepatectomized animal normal is subject to individual variation and depends also on the length of time after operation and the amount of glucose previously administered. The average animal, kept quiet in a warm room, will be maintained for an hour on 0.25 gram of glucose for each kilogram of body weight. If the animal is flaccid and 0.25 gram for each kilogram of body weight is injected intravenously, it will be restored to normal and will not need another injection for about an hour. The effect of various experimental procedures, activity, and cold, often make it necessary to repeat the injections more frequently. Furthermore, it has been found that as the length of time after operation increases, it is necessary to give more glucose. Also if a large amount of glucose is given early in an experiment, it is necessary either to maintain the same dosage or increase it.

The symptoms associated with the decreasing blood sugar following hepatectomy seem to indicate that at first there is a depression and later a stimulation of the central nervous system. The nature of this process or the component parts of the nervous system acted on has not been definitely determined. In any event the injection of glucose abolishes completely all symptoms referable to the nervous system.

The effect of glucose injection on blood pressure depends on the condition of the latter at the time of injection. If the pressure is almost normal, as it is at the beginning of an experiment, the glucose has but slight effect. If the pressure is low, as occurs after an animal has been restored many times, the glucose causes a distinct rise in pressure. The heart rate, which is always very rapid after hepatectomy, may become slower when the blood sugar is very low. If well-marked symptoms have developed the heart rate is usually irregular. The injection of glucose, regardless of the rate of heart beat, is beneficial, making it stronger and more regular. Electrocardiographic tracings have shown no change either when the animal was flaccid or after recovery following glucose injection. In some of the experiments the irregularity of the respiration is marked. Following the glucose injection the respiratory movements return to normal. The temperature may increase slightly following glucose injection but the temperature mechanism does not seem to be seriously impaired in the dehepatized animal except as it may be affected by the hypoglycemia.

Rosenthal, Licht and Melchior (189) also noted only an indirect effect of removal of the liver on the temperature

Mann and Magath (132) studied the effect of removal of the liver on geese, ducks, fishes, frogs and turtles. In each species a decrease in blood sugar occurred and some of the symptoms of hypoglycemia could be recognized but the condition was never so characteristic and consistent as in the dog. The injection of glucose produced a transitory beneficial action in geese and ducks but did not restore to normal the dehepatized animals of the other species.

*Removal of the pancreas* The classical experiments of Mering and Minkowski (156) demonstrated that total pancreatectomy produces glycosuria. Many investigators have demonstrated that hyperglycemia follows removal of the pancreas. The discovery of insulin gave the final proof of this relationship of the pancreas to the blood sugar. It is evident, therefore, that the two glands, liver and pancreas, have a reciprocal action on the concentration of sugar in the blood. If the liver is removed the sugar disappears from the blood, if the pancreas is removed the sugar increases in the blood. The decrease of blood sugar following hepatectomy is associated with definite and characteristic symptoms leading to death a few hours after the loss of hepatic function. The increase of blood sugar following pancreatectomy is also associated with definite symptoms, but death does not occur until several days or weeks after the loss of the pancreas. It became important with regard to the relation of the liver to carbohydrate metabolism to determine which effect would be produced on the blood-sugar level by the removal of both glands at varying intervals. It was essential to determine whether the liver was necessary for the more or less permanent hyperglycemia following pancreatectomy, and whether the pancreas played an important part in the hypoglycemia following hepatectomy.

While many investigations on the effect of hepatectomy and pancreatectomy have been made, few of them have included a study of the effect of removal of the two glands in relation to each other and to the blood sugar content. The work of the first investigators on hepatectomy in mammals (Bock and Hoffman (11), Schenck (197), Tangl and Harley (213)), has a bearing on the problem only as regards the fact that the technic which they employed in removing the liver

in many instances must also have damaged greatly the circulation to the pancreas. In those experiments in which the circulation was restricted to the anterior portion of the body (Seegen (204), Kaufmann (95)) both the liver and pancreas were removed functionally. In the experiments in which evisceration was employed (Kaufmann (95), Pavy and Siau (171)), the pancreas might or might not have been damaged. It is obvious that such experiments are necessarily short, and offer no opportunity to note symptoms and make other observations. It should be noted, however, that in all of these experiments a decrease in blood sugar was found.

Hédon (77) seems to have been the first to remove the liver from dogs after previously performing pancreatectomy. His results are not conclusive. Kaufmann (95) removed different portions of the viscera in normal and pancreatectomized dogs and observed the blood sugar. He was not successful in removing the entire liver and the animals were maintained under chloroform anesthesia. He records a decrease in blood sugar in both normal and pancreatectomized animals. Marcuse (138) removed the pancreas from frogs and noted marked glycosuria. He then removed the pancreas and liver simultaneously from the same species of animal and no glycosuria was observed. Kausch (96) has made the most extensive investigation of the blood sugar following removal of both the liver and pancreas. He employed geese and ducks. He first removed the liver in a series of normal fowls in a manner similar to Minkowski (157), and obtained identical results with respect to symptoms and decrease in blood sugar following hepatectomy. He then removed the liver from fowls from which the pancreas had been removed from twelve to forty-eight hours previously. He found that the blood sugar decreased even more rapidly in the fowls that had been pancreatectomized preceding the hepatectomy. He also noted that there was less glycogen in the muscle of the pancreatectomized fowls than in the normal controls, and considered this decrease in the reserve supply of carbohydrate the cause of the more precipitate decrease in blood sugar when both glands were removed.

Macleod and Pearce (115, 116) studied the results of disappearance of sugar in eviscerated dogs, normal animals, and those previously pancreatectomized. While their results were variable, they obtained

a decrease in blood sugar in both series of experiments. It should be noted that such experiments necessarily require the continuous use of anesthetics or other means of maintaining unconsciousness.

A survey of the earlier work on the blood-sugar level following removal of both liver and pancreas shows that a decrease has almost invariably occurred. However, with the exception of the experiments on ducks and geese in which the portal system anastomoses with the systemic venous system, the results of the experiments were not conclusive.

The dependence of the hyperglycemia following pancreatectomy on the liver was clearly indicated by the experiments of Mann and Magath (130). They removed the liver at various periods after pancreatectomy, observing the changes in the blood sugar level and the effect of glucose injection. Although it was found that the effect of the removal of the liver and pancreas depended somewhat on the time relations of the two procedures, the general results of the experiments were definite.

When the pancreas and liver are removed at the same operation, the resultant condition is the same as though only the liver had been removed. The blood sugar decreases, and with this decrease, the characteristic symptoms which follow hepatectomy develop. The curve of blood sugar is the same as when the liver alone is removed. The injection of glucose restores the animal to normal, usually it does not live as long after operation as when only the liver is removed, but otherwise the pancreatectomy does not seem to exert any effect on the resulting condition.

The blood sugar level is usually from two to four times greater than normal, from twenty-four to forty-eight hours after total pancreatectomy. If the liver is removed at this time the blood sugar decreases immediately and markedly. Characteristic symptoms associated with hepatectomy develop, but they appear earlier than if only the liver has been removed, and usually appear at a much higher blood-sugar level. The animal is restored to normal by the injection of glucose, but symptoms soon develop and it dies within a few hours.

The blood-sugar level usually remains fairly constant at from four to five times above normal from forty-eight to ninety-six hours after total removal of the pancreas. If the liver is removed during this



interval, the decrease in blood sugar takes place immediately and is most marked. Within two hours after hepatectomy the characteristic symptoms appear, but they develop at a blood-sugar level which, although considerably below the pre-operative level, is still above normal. The injection of glucose produces a fleeting restorative reaction, but the animal soon passes into coma and dies. Coma followed the anesthesia and hepatectomy in all animals in which the liver was removed more than ninety-six hours after total pancreatectomy.

The results of the experiments on the effect of the removal of the liver at various periods after pancreatectomy are definite. They prove conclusively that the liver is absolutely necessary for the maintenance of the blood-sugar level of the hyperglycemic, depancreatized animal in the same manner as the normal animal. The increase in blood sugar following removal of the pancreas is dependent on the presence of the liver. Without an adequate amount of functioning hepatic tissue, the increase in blood sugar following pancreatectomy could not occur. Interesting and valuable deductions have been made by Lesser (106) in reference to theoretic considerations of diabetes. Part of the basis for his deductions is the precipitate decrease in the blood-sugar level of the dehepatized depancreatized animal.

*Asphyxia and the administration of epinephrin* It has been shown that the transitory hyperglycemia that follows such procedures as asphyxia, piqûre, and the administration of drugs such as epinephrin and the general anesthetics, depends to a considerable extent on a glycogen-filled liver. Markowitz (139) has reviewed this subject and presented his own results with epinephrin. He found that the injection of epinephrin into rabbits that have been fasted always evokes extensive hyperglycemia, even when the injections are kept up for days. When the liver is glycogen free, the injection of epinephrin does not lead to hyperglycemia. When the liver contains traces of glycogen delayed hyperglycemia ensues, the extent being proportional to the amount of glycogen. It is of practical interest to know if such transitory hyperglycemia also depends on the liver. There are many data on transitory hyperglycemia which would suggest that the liver is as important in its production as in the more permanent type. Specifically, Velch (218) found that epinephrin glycosuria did not occur in frogs after removal of the liver. Collens, Shelling and Byron (28)

found that epinephrin does not influence the blood-sugar when administered in the hypoglycemic state resulting from occlusion of the arterial supply to the liver. Data bearing directly on the question of the relation of the liver to transitory hyperglycemia have been presented by Mann and Magath (131).

Data on the effect of anesthesia consisted in making a blood-sugar determination before and after the anesthesia which was given for the purpose of removing the liver. Such estimations of blood sugar have been carried out almost as a routine in all experiments on removing the liver, so that there is a large number of such observations. These data have been compared with those from a similar period of anesthesia in the same animals, given some time after removal of the liver, and with the effect of anesthesia in other animals following other operations.

The observations on asphyxia were made on some of the hepatectomized animals after the development of definite symptoms following hypoglycemia. In a few animals respiration was allowed to cease for some time before glucose was injected, and the blood sugar estimated before and after the period of asphyxia.

The series of experiments in which epinephrin was administered before and after hepatectomy was carried out as follows.

The animal was made accustomed to handling and venipuncture. After a fasting period of from sixteen to eighteen hours a specimen of blood was obtained, and the animal etherized for a period of thirty minutes, the usual time taken for removing the liver. A blood sugar estimation was made at the time the anesthetic was withdrawn and at half-hour periods subsequently. One hour afterward 0.5 cc of epinephrin (1:1000) for each kilogram of body weight, was given subcutaneously, and blood-sugar estimations were made for several hours. The resulting blood sugar curve was taken as a control curve, showing the effect of etherization and the subsequent action of epinephrin. After allowing a few days to elapse to permit the animal to recover from whatever effect the control experiment might have produced, during which time it was fed milk and syrup, the experiment was repeated in every detail except that during the period of etherization the liver was removed.

The effect of ether anesthesia and operative procedures in the pro-

duction of an increase in blood sugar is always less in an animal with an Eck fistula than in a normal animal. In fact, the majority of animals with Eck fistulas have little or no rise in the blood-sugar content following ether anesthesia. The animals in which a definite hyperglycemia does occur usually have well-developed collateral circulation to the liver. The removal of the liver always stops whatever increase in blood sugar was taking place in association with the anesthetic. In most cases the blood sugar at the time the liver is removed is the same, or but slightly greater than preceding etherization, it may be less. In every experiment the blood sugar definitely decreased, within thirty minutes after hepatectomy, below the pre-anesthetic level.

In none of the experiments did asphyxia cause an increase in blood sugar. However, it should be noted that such observations were only carried out on animals in which the blood sugar was already low and in which the glycogen content of the muscles had probably decreased more than 50 per cent over their content before operation.

The results of the experiments in which epinephrin was administered before and after anesthesia and hepatectomy are the most definite. The control period of anesthesia in each animal produced a definite increase in blood sugar. This was probably owing to the fact that in each of these animals some collateral circulation to the liver had developed. The subsequent injection of epinephrin in each animal produced marked and prolonged hyperglycemia. The maximal increase in blood sugar following epinephrin, over the preanesthetic level, was approximately 50, 70 and 100 per cent, and the duration of the hyperglycemia was from five to more than seven hours.

The effect of the epinephrin after removal of the liver was quite different from the effect with the liver intact. In some of the animals a definite increase in blood sugar occurred associated with the anesthesia and operation, although this increase was not so great as in the control experiment when only ether had been given. In other animals no increase in blood sugar was obtained. In each animal the blood sugar thirty minutes after hepatectomy was less than before etherization. In no case did the epinephrin cause an increase in the blood sugar, or in any way delay the development of the characteristic symptoms associated with the hypoglycemia. In one animal the

restoration injection of glucose maintained the animal normal for a much longer period than usual, but the usual result was obtained in the other animals. Experimental proof is therefore quite definite concerning the dependence of the transitory hyperglycemia on the presence of the liver.

*Muscle glycogen* After the liver has been removed the only considerable amount of glycogen remaining in the body is in the muscles. While the concentration of glycogen in the liver is usually higher than in the muscles, the larger bulk of the latter in the body makes the total amount of this carbohydrate stored in the two sites approximately equal. What occurred in the muscles in regard to its glycogen content after removal of the liver was a problem of great importance to be determined. Notwithstanding the extensive investigations with reference to the glycogen of muscle, only a small part has been concerned with the changes in the muscle following removal of the liver. Much of the earlier work concerned the problem of whether the muscle could make glycogen and the character of the substances which would be formed into glycogen by the muscle. The more recent work on the subject has been mainly in relation to the action of insulin. This review will include only those researches which are pertinent to studies on the dehepatized animal. Muscle can form glycogen from sugar carried to it. In perfusion experiments with the surviving muscle of the dog, Kulz (101) found that glycogen could be formed from the common monosaccharids and disaccharids by the isolated muscle. Hatcher and Wolf (76) repeated these experiments and found that glucose perfusion gave rise to an increase in the glycogen content of the perfused muscle but that other sugars were without effect. Kulz (101) injected glucose subcutaneously into dehepatized frogs and a slight increase in the glycogen content of the muscle resulted. Sachs (193) showed that the tolerance for dextrose, galactose and arabinose is not lowered by extirpation of the liver in frogs, but that a marked decrease in the tolerance for levulose occurs. Torti (215) noted an increase in the muscle glycogen of dehepatized frogs even without the injection of glucose. Laves (105) removed the livers from ducks and geese and marked diminution in the glycogen content of the muscle resulted. He was unable to demonstrate any increase in the muscle glycogen even though he fed his dehepatized animals from 20 to 30

grams of grape sugar Kausch (96) injected glucose subcutaneously into dehepatized ducks and geese and the blood sugar and muscle glycogen decreased, no evidence of glycogen formation in the dehepatized animal was obtained

De Felippi (32a) showed that there is a lowered tolerance for carbohydrate in the dogs subsequent to an Eck fistula The muscles of the animal contained a greater quantity of glycogen which is characteristic of overnutrition, and a diminished content of glycogen in the liver which is characteristic of inanition. He concluded that the muscles can form glycogen independently of the liver and that the liver is neither specific nor indispensable for carbohydrate metabolism The findings have been confirmed by Jacobson (88), who found, however, that glucose tolerance is only slightly modified in the Eck fistula animal He also concluded that the liver is not essential for the metabolism of glucose and that the muscles apparently perform well the function of glycogenesis and glycogenolysis after diversion of the portal blood from the liver

There are many reasons for the contradictory results obtained by the various observers Among these may be mentioned (1) the difficulty of obtaining standard conditions in perfusion experiments, (2) individual variation of carbohydrate metabolism in such species of animals as the frog, duck and goose, (3) the usual practically normal carbohydrate metabolism of the Eck fistula animal, and (4) the variation of glycogen content of various muscles in the normal animal, necessitating great care in comparing the muscle glycogen before and after the various procedures

A thorough study of the muscle glycogen of the dehepatized animal with and without the injection of glucose was made by Mann and Magath (131), and Bollman, Mann and Magath (17) In order that the glycogen estimation might be as valuable as possible the comparative studies were made on the same groups of muscles Care was also taken to prevent the muscles from being used much during the time of observation and to protect them from convulsions and otherwise eliminate possible sources of error All the necessary precautions, so essential in quantitative glycogen determinations, were observed The authors found that the decrease in blood sugar following hepatectomy was in every case accompanied by a corresponding marked

decrease in muscle glycogen, it did not, however, disappear entirely. The symptoms associated with the hypoglycemia appeared at a definite level of blood sugar but in the different animals the absolute amount of glycogen in the muscle bore no definite relation to the symptoms. Symptoms appeared in some animals when the glycogen content of the muscles was 0.35 per cent, and in others when it had fallen to 0.10 per cent. However, there appeared to be a relation between the glycogen content of the muscle at the time the liver was removed and the appearance of symptoms of hypoglycemia. Those animals with a high-glycogen content did not manifest symptoms as early as those with a low-glycogen content. An animal with a high-muscle-glycogen content might not manifest symptoms for ten hours after the liver was removed while an animal with low-glycogen content of the muscles might show symptoms within two hours.

When glucose was injected in the dehepatized animal after the muscle glycogen had been allowed to diminish in sufficient amounts to maintain hyperglycemia, glycogen reformed definitely in the muscle, although there was considerable variation in the amount in different muscles and even in the same muscles from opposite sides of the body. But in each instance, there was a definite increase in muscle glycogen after the hyperglycemia had been maintained for a few hours. In the experiments in which hyperglycemia was maintained by repeated injection of glucose immediately after removal of the liver, the glycogen content of the muscles decreased during the first few hours, but subsequently increased.

That glycogen is utilized by conversion to glucose in the dehepatized animal was demonstrated in the experiments in which it was injected intravenously in animals comatose from hypoglycemia following removal of the liver. The animal recovered immediately and could walk and seemed normal within a few minutes after injection. The glucose of the blood increased almost as if glucose had been injected.

Although the total amount of glycogen in the muscles is as great as, or greater than, that in the liver, muscle glycogen apparently is of little importance in the regulation of the blood-sugar level. Muscle glycogen is evidently not converted into glucose fast enough, or in a manner that will furnish glucose to the blood stream in sufficient amounts, either to produce hyperglycemia in the dehepatized animal

or to prevent such an animal from developing hypoglycemia. The dehepatized animal will die in a condition of hypoglycemia with enough glycogen in its muscles, which if converted to glucose, would maintain the blood sugar level for a considerable period. Muscle glycogen does not replace hepatic glycogen or the hepatic mechanism by which the normal level of blood sugar is maintained. It would seem as if the glycogen stores of the muscles were mainly reserved for muscular activity and the supply of sugar to the blood almost entirely dependent on the functions of the liver.

The experiments dealing with muscle glycogen in the eviscerated animal following injection of the glucose and insulin give results corresponding to those in the dehepatized animal. Cori and Cori (29) concluded that insulin increases the rate at which sugar disappears from the blood into the muscles. Best, Hoet and Mark (7) found that the muscle glycogen increased after the injection of insulin in the spinal eviscerated animal. The increase does not occur in intact animals in which insulin convulsions are permitted to occur.

*The respiratory quotient and basal metabolism.* The rapid decrease in the level of blood sugar following removal of the liver proves that there is a close relationship between tissue utilization of glucose and its production by the liver. However, it does not explain the fate of glucose in the tissues. Most of the previous investigation on the effect of removal of the liver on the respiratory quotient has been done for the purpose of obtaining data either for or against one of the important theories of the production of diabetes mellitus, the overproduction theory or the failure-to-burn-glucose theory. The principal objective in certain more recent investigations was a study of the effect of insulin on carbohydrate metabolism. The physiologic significance of the liver has usually not been the prime consideration.

Bohr and Henriques (14) studied the respiratory metabolism after ligation of the thoracic aorta, and in some instances also the inferior vena cava in dogs and rabbits. In a certain number of the experiments an increase in respiratory quotient followed. Scaffidi (196) studied the metabolism in geese in which the portal vessels were ligated, but the liver was left in the body with intact hepatic circulation. In some of his experiments an increase in respiratory quotient was noted for a few days after operation. Porges (181) investigated

the problem in rabbits, employing the following method After a fast of twenty-four to forty-eight hours, the animal was given urethane When under the influence of the drug, the abdominal aorta, the inferior vena cava, and the hepatic and portal veins were ligated After a short period, in order to exclude the immediate effects of the operation, tests were made Only a small portion of the experiments were successful, these showed an increase in the respiratory quotient Porges and Salomon (182) performed similar experiments on animals in which the pancreas had been removed one to two days preceding the ligation of the abdominal blood supply In these animals also the respiratory quotient increased after the latter procedure Grafe and Fischler (69) did not find any change in the respiratory metabolism following Eck fistula except in the stage of intoxication Verzar (219) injected starch and dextrose solution in animals in which he had eliminated the liver from the portal circulation, and demonstrated that the carbohydrates were burned Rolly (187), employing the same operative procedure as Porges, obtained similar results, but attributed the increase in respiratory quotient to changes in reaction of the blood Bohm (13) found but a slight rise in the respiratory quotient after exclusion of the abdominal organs following pancreatectomy Fischler and Grafe (51) studied the respiratory exchange following the ligation of the hepatic artery in dogs in which an Eck fistula had been performed some weeks previously In most of these experiments there was an increase in the respiratory quotient Murlin, Edelmann and Kramer (166) studied the respiratory exchange and gas content of the blood after occlusion of the abdominal aorta and inferior vena cava in dogs The results with reference to the respiratory quotient were variable, but in each instance the blood gas changes were consistent with the altered respiratory quotient These authors review critically all previous work on the problem and conclude that the obstruction of the blood to and from the abdominal organs does not alter the metabolism, and that all the results can be explained on a mechanical basis Grafe and Denecke (68) studied the gaseous metabolism in geese and dogs They removed the liver in dogs by performing an Eck fistula and after a considerable period removed the liver lobe by lobe They found that heat production was always decreased



A study of the respiratory quotient, total heat production, and the effect of injection of glucose has been made by Mann and Magath (131). They used the method described in detail by Kitchen (97) and also briefly described by Boothby and Sandiford (20). It is an adaptation for use on dogs of the same technic that has been so carefully developed and fully described by Boothby and Sandiford (19) for man. In experiments of this nature in which it is necessary to determine the respiratory quotient and heat production over many successive short periods, and after various procedures, only the indirect calorimeter method can be employed. The important points in the work on the dog are as follows: (1) careful selection of the subject, (2) accurate control of the diet and environmental factors in the laboratory, (3) careful training of the subject, (4) the development of a special mask, and (5) the carrying out of the careful metabolism technic, described by Boothby and Sandiford (19).

Great care was used to select dogs that were quiet and gave promise of being capable of being trained. They were placed on an approximately constant diet which would just maintain their body weight. They were always fed at approximately the same time each day which permitted a fast of sixteen to eighteen hours before beginning the succeeding tests. In the first period of training the dog was placed on the table for an hour or so, with feet held in place by a restraining strap. Next the mask was placed on the head without being adjusted. Finally the animal was trained to lie quietly for hours at a time with the mask adjusted for observations. If at any state of its training the animal was found unfit for metabolism work, it was discarded. The mask is a hollow cylindrical cone of copper sheeting, open at the base and having inlet and outlet tubes at the apex. The animal's head is placed in the mask and the opening around the neck made air-tight with a carefully placed rubber dam.

It should be emphasized that if metabolism work of this nature is to be of any value, the animal must be perfectly quiet for a considerable period preceding as well as during the test. The usual time for collecting the air was fifteen minutes. Pulse, respiration and temperature were carefully noted during this time. Also the animal was closely observed. If any movements occurred, the tests were unsatisfactory and were not considered of value in drawing conclusions. The routine procedure in these experiments was as follows.

The two preliminary operations for removal of the liver as previously described were performed. The animal was then carefully trained for metabolism work. Several preliminary tests were carried out and when the successive tests checked quite closely, the final experiment was performed. In some animals the effect of the injection of definite amounts of glucose was obtained preceding the final experiment. On the day of the final experiment, two or more tests were made. The animal was then etherized and the liver removed quickly. Tests were made at various periods after the operation, when the animal was moribund, and after the injection of various amounts of glucose when it was in the moribund condition. Following glucose injection, tests were made at five minutes, thirty minutes, sixty minutes and ninety minutes. Blood-sugar estimations were made at various intervals, when the procedure employed to obtain the blood would not in any way disturb the animal for the metabolism tests. The first tests were made long enough after the withdrawal of the ether apparently to eliminate it as a significant complicating factor.

The results of the experiments, while on the whole constant enough to permit suggestive conclusions, were not entirely satisfactory. As may readily be surmised from the highly technical character of the investigation it was exceedingly difficult to carry it out satisfactorily in all respects. The pre-operative tests, while checking fairly closely were not as constant as in many other normal animals used in metabolism work. This appeared to be due to various causes. In metabolism work on animals, in order to obtain the best results, it is important to select the proper animal because in order to obtain consistent results, the dog must be well trained. Since it was necessary to perform two preliminary experiments before beginning observations, the range of choice was greatly decreased. Some of the animals were not wholly suitable for metabolism work, some that had been satisfactory in the pre-operative observations, were too restless following removal of the liver to be suitable. It was found exceedingly difficult to maintain the operative animal near a basal rate.

The injection of glucose before operation produced but slight response. The injection of 0.25 gram of glucose for each kilogram of body weight showed little or no change in the total heat produced and the respiratory quotient was but slightly increased. When 0.5 gram

of glucose for each kilogram was used, the total heat produced sometimes increased slightly, and there was always a small but definite increase in respiratory quotient. The administration of 1 gram or more of glucose for each kilogram of body weight always produced an increase in respiratory quotient and total heat production. After the liver was removed the respiratory quotient was increased in those tests made when the animal was seemingly in a normal condition. When it became moribund the respiratory quotient might decrease to the level preceding operation. It always increased following the injection of glucose after hepatectomy, such increase was always apparent in the first test beginning five minutes after the administration of the glucose. Usually the response with regard to the respiratory quotient was greater following a given amount of glucose to the hepatectomized animal when compared to the control injection preceding operation, but this was not always the case.

Whether the total heat production changed after hepatectomy depended to some extent on concomitant factors other than the loss of hepatic tissue. If the animal remained quiet after operation the total calories produced decreased. This was the usual response. If the animal became restless after operation the heat production remained the same or increased. The total caloric output was increased in the tests on animals in the moribund condition associated with muscular twitching. There was always an immediate increase in the heat production following the injection of glucose and as was noted in the case of respiratory quotient, the same amount of glucose often caused a greater increase in total heat production after hepatectomy than before.

Burn and Dale (23) in a research which was primarily for the purpose of determining the action of insulin, found that the respiratory quotient of the decapitated and eviscerated cat was unity. Similar results were obtained by Best, Dale, Hoet and Marks (6). The results of the experiments on the dehepatized animal indicate that when the liver is removed the respiratory quotient increases and approaches unity. Care must be exercised in drawing conclusions from such results, however, because in none of the experiments could it be definitely proved that the animal was in a basal condition following the removal or exclusion of the liver. The effects of the anesthetic or narcotic and operation were not eliminated.

*The effect of insulin* The discovery of insulin, the active principle of the islands of the pancreas, by Banting and Best (3) gave renewed impetus to the study of carbohydrate metabolism and particularly of the blood sugar. The enormous amount of work that has been done on insulin is well reviewed in Macleod's (113) monograph and it need only be mentioned here. Only one phase of the main problem associated with the action of insulin is pertinent, the relation of the liver to the hypoglycemic action of insulin.

It was shown by Mann, and Magath (128, 129), that following total removal of the liver (1) a decrease in blood sugar always occurs, (2) the hypoglycemia is always accompanied by a characteristic group of symptoms, and (3) the administration of glucose abolishes the symptoms and temporarily restores the animal to normal. The discoverers of insulin found that (1) its administration is followed by hypoglycemia, (2) a characteristic group of symptoms developed, and (3) glucose is effective in relieving the symptoms. There is, therefore, a close similarity between the effect of removal of the liver and the administration of insulin.

The problem of whether the liver is responsible in whole or in part for the hypoglycemic action of insulin was investigated by Mann and Magath (133). They found that the curve of blood sugar in the dehepatized animal is characteristic and, while differing somewhat in degree, is comparable in the different animals. A control curve of blood sugar could be obtained by the administration of insulin before the liver was removed, and if the amount of insulin given were sufficient, a much more precipitate decrease in blood sugar would be produced by the insulin than by removal of the liver. If the administration of the same amount of insulin after removal of the liver did not alter the blood-sugar curve from that usually occurring in the dehepatized animal, it would be evidence that the liver is of importance in the hypoglycemic action of insulin. On the other hand, if the curve of blood sugar following the administration of insulin was not affected by dehepatization it would show that the presence of the liver is not necessary for the hypoglycemic action of insulin. Experiments were performed as follows. The animal, prepared by previous operations for removal of the liver, was fasted for from sixteen to eighteen hours. Two or more blood-sugar estimations were made at

half-hour intervals to obtain the normal blood-sugar level. Insulin was then injected intravenously. In order to determine whether there was a difference in the action of insulin before and after removal of the liver, it was necessary to obtain a more precipitate curve following the administration of insulin. Blood-sugar determinations were made at frequent intervals afterward, and the condition of the animal noted. In instances in which symptoms developed, and it was necessary, glucose was administered and the determination of blood sugar made until the animal had been apparently normal for two or more hours. After a variable period, from one to four days after the experiment, the animal was again fasted, a normal blood-sugar determination made, and the liver totally removed. Blood-sugar determinations were made at short intervals following the operation. When the animal had recovered from the immediate effects of the anesthetic and operative procedures, usually within an hour, the same amount of insulin was injected as in the experiment before the removal of the liver. Blood-sugar determinations were made at practically the same intervals as in the control experiment. The condition of the animal was again carefully noted, and when necessary, glucose was injected. The experiment was thus maintained for several hours after operation. In one experiment insulin was not administered before the liver was totally removed, and only the procedures following removal were employed. This experiment was performed in order to determine whether the insulin administered before removal influenced the blood sugar and action of insulin after removal. In order to make the blood-sugar curves following the administration of insulin before and after operation more comparable, in one experiment anesthesia was induced before the control injection of insulin for the same length of time as was necessary for the partial removal of the liver.

The results of these experiments to determine whether or not the hypoglycemic action of insulin is necessarily dependent on the liver, are definite. The injection of large doses of insulin into dogs before total removal of the liver produced marked hypoglycemia, the decrease in blood sugar was much more rapid than occurs after removal of the liver. In some of the animals symptoms developed which were, in the main, identical with those occurring with the hypoglycemia following loss of liver, and the injection of glucose produced the same

immediate restoration to normal. Slight symptoms only followed the injection of insulin in some animals, and although the blood sugar decreased to a very low level, the animal recovered without the administration of glucose.

The administration of insulin after total removal of the liver produced the same precipitate decrease in blood sugar as with the liver intact. The hypoglycemia occurred much more quickly, and the symptoms, when they were present, were the same as if insulin had not been injected and only hepatectomy performed. The intravenous injection of glucose in the experiments following total hepatectomy and administration of insulin produced the same quick response, but when the liver was intact, the blood-sugar level was gradually restored and then maintained at normal, whereas when the liver had been removed, the hypoglycemia and the associated symptoms recurred, making repeated injections necessary. The length of time a given amount of glucose maintained the animal following the injection of insulin after removal of the liver was variable.

Burn and Dale (23) found that insulin produced the characteristic fall of blood sugar in the decapitated and eviscerated cat in which a constant infusion of dextrose was being made. Best, Dale, Hoet and Marks (6) found that the glucose which disappears from an eviscerated spinal animal under the action of insulin is equal to the sum of the glycogen deposited in the muscles and the glucose equivalent of the oxygen absorbed.

It is quite evident that the presence of the liver is not necessary for the hypoglycemic action of insulin. On the other hand, the presence of the liver is necessary for the permanent recovery of the blood-sugar level. This does not necessarily mean that the liver may not play a part in the production of the hypoglycemia of insulin. The fact that the liver is essential for the restoration of the normal blood-sugar level proves that this organ is affected either directly or indirectly by the insulin.

*Urea and amino acids* Since the synthesis of urea and deamination are so intimately related, the effect of removal of the liver on these two processes will be discussed together. However, the possibility is recognized, as emphasized by Fearon (44), that the two processes may not necessarily be concomitant. There have been many debated

problems concerning urea from the time of the discovery of its importance in nitrogenous metabolism by Rouille to that of the latest review of its biochemistry by Fearon. Among these problems none has given origin to more research than that concerning the site and nature of the transformation of nitrogenous metabolic products to urea. Three different answers have been made by the various investigators of the problem. Since urea has such a wide biologic distribution, being found in the very lowest forms of animal life and even in some plants, it would seem that its formation should be considered as one of the more fundamental processes of metabolism and thus be a property of all cells. This consideration has logically led to the view that deamination and the formation of urea occur in all the tissues and are properties of all the body cells. Many investigators seemed to formulate this answer to the problem. However, the significance of the portal circulation in the higher forms of animal life whereby the absorbed products of protein digestion must pass through the liver before reaching the other tissues of the body led to the consideration of the liver as being the specific organ for performing this process. The results of much of the earlier work tended to support the view that the liver was of more importance in this respect than many of the other organs. As the results were indeterminate for a long time and both views appeared to have substantial supporting data, it appeared possible that both views were correct—that is, deamination and the formation of urea occurred in all tissues but the liver had specific ability in regard to the two processes.

While this discussion is concerned specifically with the results of removal of the liver on deamination and urea formation, it is of value to review briefly the data obtained by other closely related methods of approach. Among these are included (1) comparison of urea content of the arterial and venous blood of the various tissues, (2) a comparison of the urea content of various tissues, (3) perfusion of organs with or without some of the precursors of urea, (4) a comparison of the urea content of various autolyzed tissues, (5) studies of clinical cases of hepatic disease, (6) studies on animals after the administration of various hepatic poisons, and (7) the effect of removal of various organs, especially the liver.

Poiseuille and Gobley (179) were the first to compare the urea

content of arterial with venous blood. Using their own method for the determination of urea, they found that the venous blood to a certain organ sometimes contained more, and sometimes less urea than the arterial blood. Gescheidlen (72) concluded that there is little difference between the urea content of arterial and venous blood, even of that passing through the liver. At first Picard (177) found similar amounts in both artery and vein, but later more urea in the vein than in the corresponding artery. Grehant and Quinquaud (71) found that the arterial and venous blood from the head or extremities contained the same amount of urea, but that the venous blood from the liver or spleen was richer in urea than the arterial blood. They concluded that urea was formed by the abdominal organs. Kaufmann (94) observed no difference between the urea content of arterial and venous blood in the dog and horse.

Taylor and Lewis (214) removed all the abdominal viscera, except the liver, from dogs, leaving the arterial supply to the liver intact. By comparing the urea content of the peripheral blood with that of the hepatic vein, they found no evidence of the liver having any special function in the formation of urea.

Heynsius (79) found urea in the normal mammalian liver in considerable amounts, Stokvis (211) confirmed this, and added that urea was probably formed from uric acid in the mammalian liver. Meissner (153) found uric acid in the liver of birds, and urea in the liver of mammals. He concluded that urea was formed in the liver from the products of the disintegration of blood cells destroyed in the liver.

Gescheidlen (72) found the urea content of the different organs of the dog to be about the same as that of the blood, and concluded that the liver was not the sole source of urea. His findings were confirmed by Munk (165) who used different and better methods for the determination of urea. Pekelharing (173) directed attention to errors in Munk's methods but Hoppe-Seyler (83) found that little urea was formed in the liver after death, and was unable to find either leucin or tyrosin in the normal liver or blood. They, therefore, concluded that these substances were not precursors of urea. Kaufmann (94) found that the blood contained less urea than the tissues, but the liver and spleen more than the muscles. Schondorff (199) discovered that the urea content of the blood and tissues was about the same, the urea



content of the muscles being slightly lower Herter (80) estimated the urea content of the liver to be twice that of the muscles or brain

Folin and Denis (58), studying the absorption and distribution of various nitrogenous substances, found that the urea content of the muscles was slightly higher than the urea content of the blood They proved that urea, amino acids, creatinin, and so forth, were absorbed by the various tissues Using cats in which the blood vessels to the kidneys had been ligated, they found that, following absorption of amino acids in the muscles, the urea content of the muscles increased, whereas the non-protein nitrogen decreased.

Van Slyke and Meyer (217) confirmed Folin and Denis' (58) results, but found that the liver absorbed more amino acids and liberated them sooner than the muscles The urea content of the blood increased with the decrease in amino acids in the liver, accordingly these authors, differing from Folin and Denis concluded that the liver was especially responsible for the formation of urea

Marshall and Davis (140) found that the urea content of the tissues was approximately that of the blood, and that the injection of large amounts of urea increased the urea content in about equal proportion, except for the lesser amounts in fatty tissues and the larger amounts in tissues in contact with the urine

Cathcart (25) found that ammonia and glycocoll injections in dogs greatly increased the urea content in the liver and somewhat in the muscles, and concluded that urea formed from these substances

Cyon (31) found that perfusion of liquid through the liver enriched the fluid in urea. Gescheidlen (72) showed this to be a mechanical washing out of the urea in the liver Von Knieriem (98) found that ammonium salts were converted into the urea in the body, and the details of the building of urea by combination of ammonia and carbonates was shown by Schmiedeberg (198), who used Ludwig's method of perfusing the liver. Von Schroder (200), by using ammonium carbonate in his perfusate, demonstrated the conversion of this substance into urea in the liver. He was unable to demonstrate any conversion in the kidneys or muscles, and concluded that the formation of urea, especially from ammonium carbonate, is a function of the liver alone Salaskin (194), using glycocoll, leucin and asparagin in perfusion of the liver, obtained a transformation of these substances

into urea This was also accomplished with many other amino acids by Embden, Salomon and Schmidt (40) Fiske and Karsner (48) found that ammonia was readily converted into urea in the surviving liver, but that glycocoll was not changed They also found that the liver, poisoned by various toxic agents, retained its power of converting ammonia into urea Jansen (90), however, found that the perfused liver did form urea from glycocoll, and concluded that the liver played an important part in the formation of urea from amino acids He further showed that urea was produced even though the perfusate was already rich in urea, and concluded that this was not a reversible process in the liver Löffler (110) found leucin, alanin, glycin, aspartic acid and serin converted to urea by the perfused liver Tyrosin, cystin and taurin were not so changed Felix and Tomita (45) found arginin converted to urea in the liver of the cat

Kossel and Dakin (100) found arginase in large amounts in the liver of mammals, none in the muscles, and only small amounts in the kidneys and lymph nodes Fosse and Rouchelman (61) found the urea content of the autolyzed liver (dog) to be greatly increased over that of the autolyzed heated liver Hoagland and Mansfield (81) incubated muscle aseptically for several days and found no increase in urea content Levene and Meyer (107) likewise found no diamini-zation of amino acids incubated with leukocytes or renal tissue Hammett (75) found that incubation of pulped placental tissue increased the urea content of the digesting mixture

Frerichs (64), studying acute yellow atrophy, attributed the appearance of leucin and tyrosin in the urine to a cessation of the function of the liver in the formation of urea, and thought the nervous phenomenon accompanying this disease due to the cessation of protein metabolism with the accumulation of toxic products in the blood Winterberg and Munzer (231) studied the results of urinalysis in many diseases of the liver, acute yellow atrophy, infectious jaundice, atrophic and hypertrophic cirrhosis, and found little evidence to indicate that the liver was the sole site of urea formation

Frey (65) reports an extensive review of the literature, and includes his own clinical data on urea and ammonia excretion in diseases of the liver

Stadie and Van Slyke (209) report a case of acute yellow atrophy in

which the urine showed a low urea content with a high ammonia and amino-acid content. The blood contained a low value for urea, and the amino-acid content was high. Gilbert, Chabrol and Bénard (66) found high values of urea in the blood of patients with extensive blood destruction and jaundice. These authors concluded that the liver was responsible for the production of urea, as in the atrophy the function was diminished and the formation of urea decreased, while in anemia the function was increased by the blood destruction, and the urea production increased.

Fohn and Berglund (56) found that ingestion of amino acids in normal human subjects was followed by an increase of the amino-acid content of the blood, and increased excretion of amino acids in the urine. The urea content of the blood did not increase until the amino-acid content had begun to fall, and the excretion of amino acids had returned to normal. The authors consider this to be evidence that the liver has no special function in the formation of urea, but that urea is formed by all the tissues.

Most of the investigations on nitrogenous metabolism following the administration of the various hepatic poisons have given inconclusive results. Pearce and Jackson (172) found that the necrosis of the liver which follows the injection of hematoxic immune serum is associated with increased elimination of total nitrogen, augmented output of urea and slight change in ammonia. Marshall and Rowntree (141) studied the effect of chloroform and phosphorus in dogs and noted among other changes, an increase in the amino nitrogen and decrease in the urea of the urine, especially after chloroform. Lewis and Izume (108) found that after the administration of hydrazin there was a rise in the amino-acid content of the blood without an increase in urea when the kidneys were unaffected. In the hydrazin poisoned animal the power to metabolize injected glycine, to transform glycine into glucose and urea and to synthesize glycogen from glycine, was diminished. These results are ascribed to the derangement of the functions of the liver.

The futility of methods which attempt to determine the site of urea formation by comparison of the urea content of the blood flowing to an organ or tissue with the urea content of the blood flowing from the same tissue is readily seen by a consideration of the total amount of urea produced in relation to the flow of blood from the organ or tissue.

If the amount of urea produced at any given time is compared with the flow of blood at the same time, it is evident that the present chemical methods are inadequate to determine the change in urea concentration. There is no doubt that urea is widely and fairly uniformly distributed throughout the body, and probably all bodily secretions contain it in amounts comparable to that in the blood. The equal distribution of urea is so constant that Hensch and Aldrich (78) were able to estimate the amount in the blood by the determination of that in the saliva. Owing to its solubility and diffusibility, it is rapidly absorbed by all the tissues. For this reason any conclusions with regard to the site of its formation drawn from tissue analysis, must be open to question. Methods of artificial perfusion of organs have serious objectionable features, as previously discussed. Conclusions based on studies of extensive hepatic disease indicate that the liver has a marked influence on the production of urea, but no definite conclusions seem possible. The extent of the lesions and the functional capacity of the liver may vary extensively, and the influence on other tissues is always to be considered. The same criticism applies to most of the studies in which hepatic poisons were used.

It was easily proved that the kidneys were not responsible for the formation of urea. Prevost and Dumas (184) isolated urea from the blood after extirpation of the kidneys and numerous investigators have shown that the urea content of the blood and tissues is independent of the kidneys, which are merely the excretory organs for that substance.

Nebelthau (168) was unable to find any urea in the urine secreted after the removal of the livers in frogs, although he did find a marked increase in the ammonia excreted. Moleschott (160) found it still present in the muscles of frogs several days after the liver had been removed. Poulsson (183), after removing the livers of frogs and injecting ammonium salts in the lymph sacs, found that the urine contained considerable urea.

Stadeler and Frerichs (208) found the various tissues of sharks to be exceedingly rich in urea. Von Schroder (200) extirpated the livers of sharks and found that the high urea content of the muscles was unaffected. He attributed this to the failure of the kidneys to secrete urine, rather than to the removal of the liver.

Minkowski (157) removed the livers from geese and studied the nitrogen elimination extensively. A marked decrease in the uric acid excretion and an increase in ammonia excretion resulted. The urea excretion decreased following hepatectomy, and it was not increased by injections of large amounts of amino acids, although the ammonia excretion was increased. Urea injected subcutaneously was excreted unchanged.

Von Schroder (201) showed the formation of urea from ammonium carbonate in nephrectomized dogs. He then closed the blood supply to the liver by ligating the hepatic artery and the hepatic veins, anastomosed the portal vein to the left renal vein, and extirpated the kidneys. His animals lived about two hours, during which time no increase in urea in the blood was observed, even after the injection of ammonium salts. In some cases there was a decrease in the urea content of the blood.

Slosse (206) ligated the celiac and both mesenteric arteries. This caused considerable decrease in the amount of urea excreted by dogs surviving for from four to fourteen hours after operation. He concluded that the abdominal organs exercised considerable influence on the formation of urea. Hahn, Massen, Nencki and Pawlow (74) ligated the hepatic artery in dogs subjected to Eck's fistula. The urine of these animals contained increased amounts of ammonia, and a decrease in the urea excretion was observed.

Lieblein (109), using Pick's method of removing the liver (injection of sulphuric acid into the bile ducts), found that the urine of dogs so treated contained large amounts of uric acid. The urea excretion was little altered, but the ammonia excretion was markedly increased.

Kaufmann (94) ligated the aorta and vena cava in the thorax (method of Bock and Hoffman (11) and Seegen (204)), and kept dogs alive for from an hour to an hour and a half by artificial respiration. He noted a slight increase in the urea content of the blood in some cases but not in others.

Doyon and Dufourt (35) ligated the hepatic artery and portal vein after partial removal of the liver, with the result that the excretion of urea was markedly lower in relation to the total nitrogen excreted. Injury to the liver resulted in a decrease but not in complete cessation, of the formation of urea. The ammonia excretion was relatively increased.

Salaskin (195) ligated the hepatic artery in dogs with Eck's fistula, the urea excretion decreased with the increase in ammonia in the urine. Biedl and Winterberg (9) observed that animals with Eck fistula, during meat intoxication, secreted increased amounts of ammonia and excreted decreased amounts of urea. They further found that injected ammonia was excreted as urea to some extent after ligation of the hepatic artery in these animals. Horodynski, Salaskin and Zaleski (84) confirmed Biedl and Winterberg's (9) results, but their conclusion differed in the belief that the liver is entirely responsible for the formation of urea from ammonia.

Fiske and Sumner (49) excluded the liver in cats by ligation of the celiac and mesenteric arteries, then the portal vein and hepatic artery, and after ligation of the kidneys found an increase in urea in the blood and muscle. After the injection of amino acids these animals showed increase in the urea content of the muscles and blood. The increase was not marked, and observations extended over a short period only (three hours) during which the animal was kept alive by artificial respiration.

Matthews and Nelson (145) injected amino-acid mixtures intramuscularly into dogs with Eck fistula after ligation of the hepatic and mesenteric arteries. They maintained diuresis by the injection of considerable amounts of diuretic fluids, and obtained a slight increase in the amount of urea excreted over that excreted by the control animals with no amino-acid injection. They obtained similar results by removing the entire abdominal viscera, leaving from 20 to 25 grams of hepatic tissue adherent to the vena cava. The amount of urea excreted decreased markedly in all their experiments after the liver was removed, and in some cases they obtained a slight rise again after injection of the amino-acid mixture.

Perroncito (175) removed most of the liver from dogs with Eck fistula, leaving only traces attached to the vena cava. His animals recovered and seemed normal for a few hours. He noticed a diminution in the amount of urea excreted, and also a fall in blood urea, except in one case in which a piece of liver had been allowed to remain free in the peritoneum.

Von Falkenhausen and Siwon (42) extended the observations of Minkowski on the deamination of amino acids in hepatectomized

geese. They injected large amounts of amino acids into geese after removing the liver and found that the amount of ammonia excreted was greatly increased, but that no formation of urea could be determined. After comparing these findings to those obtained in normal geese after injections of amino acids, they concluded that the liver does not play a part in all phases of the intermediary metabolism of proteins and that especially in the deaminization of proteins it was not concerned. With the injection of large amounts of amino acids into the circulation, the production of ammonia takes place at the same rate whether the liver is excluded or not. On the contrary, the synthesis of urea appears to be an exclusive function of the liver.

Morgulis (162) estimated the urea and amino-acid content of the blood at definite intervals following the ingestion of a standardized protein diet. He found only slight changes in the well-fed animal, but after a prolonged fast the blood urea rose immediately after the meal although increases in the amino-acid content of the blood were not found until later. In dogs with an Eck fistula the urea changes were similar but the amino-acid increases were found within the first hour. He presented the data as evidence that the liver is the site of formation of urea, since the blood urea was found to rise before increases could be determined in the amino-acid content of the blood after the feeding of a protein meal.

Many studies have been made with special reference to the relation of ammonia to urea. Folin and Denis (59) demonstrated the relative unimportance of ammonia, which was formed in the intestine and absorbed into the portal vein. Nash and Benedict (167) almost eliminated ammonia from consideration when they demonstrated the formation of ammonia to be a function of the kidney, although Bliss (10) has recently reaffirmed that ammonia is a product of the activity of all tissues. The experiments of Rich (185) indicate that the methods employed for removal of the liver by ligation of its main blood supply are ineffective in completely obliterating the liver. The results of experiments when the liver was not entirely removed should not be interpreted as meaning complete suppression of the function of that organ.

The importance of the liver in the formation of urea and deaminization was conclusively demonstrated by Bollman, Mann and Magath

(15, 18) in studies on the dehepatized dog. Four series of experiments were performed, three dealing mainly with the formation of urea and one with deaminization. In one series of experiments the liver was removed and the normal appearing condition of the animal and secretion of urine maintained by the appropriate administration of glucose. In the second series of experiments the kidneys were also removed at the same time the liver was removed. In the third series of experiments the kidneys were removed and a few hours later, after a substantial increase in blood urea had occurred, the liver was removed. In the fourth series of experiments, amino acids were injected into the animal before and after removal of the liver.

The results of the experiments were definite and conclusive. When the secretion of urine was maintained in the dehepatized animal there was a marked and progressive decrease in the urea of the blood and tissues and the amount of urea excreted in the urine showed a marked relative and absolute progressive decrease, so that after a few hours the blood, urine and tissues contained only minimal amounts of the substance. If both kidneys and the liver were removed at the same time the urea content of the blood and tissues remained constant at the amount present before operation. If the kidneys were removed first, and after a definite increase in blood urea had taken place, the liver was removed, no further increase in urea occurred.

Following removal of the liver there is always an increase in the amino-acid nitrogen content of the blood, urine and tissues. The increase in amino-acid excretion in the urine is subject to rather wide variations and is dependent on the factors influencing the excretion of urine. Usually the hourly rate of excretion of amino-acid nitrogen in the urine more than doubled following removal of the liver and remained fairly constant so long as the urine was being excreted. The increase of amino-acid nitrogen of the blood following removal of the liver is also subject to some variation but an increase is always found a few hours after operation and the amount progressively increases. There is always a great increase in the amino-acid nitrogen content of the muscles in the dehepatized animal. Removal of the kidneys of the dehepatized animal produces a greater increase in the amino-acid content of the blood and tissues.

The series of experiments in which amino acids were injected before



and after removal of the liver were decisive. If amino acid as glycoll or alanin is injected intravenously into a normal animal, a rapid conversion of the amino acids to urea occurs. The amino-acid content of the blood quickly increases and then progressively decreases, returning to the normal level in about two hours. The amino-acid content of the urine is greatly increased during the same period the amino content of the blood is above normal and approximately 20 per cent of the amino-acid nitrogen is excreted unchanged in the urine. Blood urea and urinary output of urea is also greatly increased for a slightly longer period. About 25 per cent of the nitrogen injected is found as additional urea in the urine. The increase in the urea nitrogen of the blood and tissues together with the amino-acid nitrogen and urea excreted by the tissues is sufficient to account for almost all the amino-acid nitrogen injected if the urea is considered as being equally diffused throughout the body. The effect of injection of amino acids into a dehepatized animal is quite different from that in a normal animal.

The intravenous or enteral administration of amino acids to dehepatized animals increases the amino-acid content of the blood, urine and tissues. Immediately following intravenous injection of amino acids a large amount of the amino-acid nitrogen is present in the blood. Its concentration subsequently diminishes so that six hours after the injection, the amino-acid content of the blood is only slightly greater than the amount usually found in dehepatized animals at that interval after operation. The amino-acid content of the urine is increased following its administration to dehepatized animals, usually about one-third of the amount administered is recovered unchanged in the urine. The amount which is not recovered in the urine is easily accounted for by the increase in the content of the muscles, since the concentration of the acid is much higher than that which obtains in the uninjected animal. It is in fact sufficiently high to account for all of the injected amino-acid nitrogen which has not been excreted in the urine. Enteral administration of amino acids produces essentially the same changes in the hepatectomized animal as are produced by similar intravenous injections, except that the amino-acid content of the blood is not raised to such a high level.

Besides the complete recovery of unchanged amino acids following

injection into the dehepatized animal, there is substantial evidence to show that amino acids are not destroyed in the absence of the liver. The administration of amino acids does not alter the urea content of the blood, tissues or urine of the dehepatized animal, and the entire amount of urea excreted during the life of these animals is only the equivalent of the decrease in the urea content of the tissues after removal of the liver. Even if no urea is excreted following removal of the liver, the urea content of the blood and tissues cannot be increased by the administration of amino acids for more than fifteen hours, the length of time the animal lives. It is evident, therefore, that no urea is formed in the dehepatized animal even after the injection of large amounts of amino acids. Nor is there evidence of formation of glucose from amino acids in the absence of the liver. Following hepatectomy the sugar content of the blood decreases progressively so that symptoms of hypoglycemia develop within a few hours after operation and the animal will die from hypoglycemia in from three to ten hours unless glucose, or some sugar which is convertible to glucose, is administered. The administration of amino acids, particularly glycocoll or alanin, is without effect in altering the course of the hypoglycemia of dehepatization.

The striking decrease in the urea content of the blood and tissues, with the equally striking decrease in the urea excretion, proves conclusively that there is a marked decrease in the amount of urea formed in the body following removal of the liver. The progressive decrease in urea to such a minimal amount in both blood and urine is so marked as to indicate strongly that urea formation ceases immediately following hepatectomy. Although it is difficult to estimate accurately the total amount of urea present in the body at the time of operation, the total amount excreted from the body afterward is within a few milligrams of that which can be accounted for by the decrease in the urea content of the blood and tissues, without the formation of more urea. The excretion of ammonia by these animals is entirely inadequate to account for the diminution in the urea excreted, for the total ammonia excretion is markedly lowered with the low urea excretion, although the relative amount of ammonia excreted is increased. Further, in the animals in which the liver and kidneys were removed, the increase of ammonia in the blood was inconsiderable, and there was no increase in urea.

In animals that remained anuric, or in which the kidneys were removed at the time the liver was removed, the urea content of the blood and tissues remained constant until the conclusion of the experiment, as long as twelve hours. All control animals, in which bilateral nephrectomy was performed, exhibited the usual marked rise in the urea content of the blood and tissues, but if the liver was subsequently removed from these animals no further rise could be detected, and the urea remained constant at this high level.

It may be stated definitely that deamination of amino acids in the dog depends directly on the presence of the liver. All evidence thus far may not be interpreted in any other manner. In the dehepatized dog there is an accumulation of amino-acid nitrogen which is comparable in amount to the nitrogen changed to urea by the normal fasting animal. In the dehepatized dog there is no measurable amount of urea formed. The ammonia formed following hepatectomy seems to be almost entirely dependent on the conversion of the urea present at the time of removal of the liver, since the excretion of ammonia of the hepatectomized animal decreases greatly with the decreased amount of urea in the urine and since the administration of amino acid does not alter this decrease. Since evidence has not been obtained of the formation of glucose from the amino acids in the liverless dog it would appear that evidence of the formation of any of the products of deamination in the hepatectomized animal has not been obtained. Following the injection of amino acids into these animals, they not only demonstrated the absence of any of the products of deamination but also demonstrated that the entire amount injected remains unchanged in the blood, urine, and tissues of the animal many hours after administration. Comparison of these facts with the metabolism of amino acids in the normal animal adds emphasis to the conclusion that no deamination occurs in the dog after the liver has been removed.

*Uric acid.* Uric acid metabolism has offered several difficult problems. On the clinical side is gout with its definite but as yet undetermined changes in the normal sequence of events in the process of uric acid metabolism and elimination. A comprehensive view of the physiologic aspects of the subject is made difficult because of the variation in the production, elimination or destruction in the various

species of animals In certain species practically all nitrogen is eliminated in the form of uric acid while in other species the uric acid produced is almost wholly destroyed The work done on the hepatic relationship to this substance is reviewed, not because of its possible immediate value to clinical medicine but in order to present certain phases of its comparative physiology

Only the investigations dealing with the possible relationship of the liver to uric acid metabolism will be considered A general review of uric acid metabolism has been included in previous studies (Folin (55) and Benedict (4))

Minłowski (157) found a marked decrease in the uric-acid content of the urine of geese following hepatectomy The administration of urea to these animals did not increase uric acid excretion, as it does in normal birds, this clearly demonstrates that the power of synthesis of uric acid from urea is lost when the liver is removed Von Mach (112) after repeating these experiments, pointed out that the uric acid did not entirely disappear from the urine of hepatectomized birds owing to the two sources of the acid in these animals, namely, throughout the body, from metabolic processes, and in the liver, from synthesis from urea which takes place in this organ only

That the liver of mammals also plays some part in the metabolism of uric acid was demonstrated by Pawlow and his pupils (74) in studies of the urine of dogs following the production of Eck fistula They found that such animals excreted a greater amount of uric acid, which they attributed to a failure of the liver to oxidize uric acid Adberhalden, London and Schittenhelm (1) found that this increase in the excretion of uric acid was compensated for by a corresponding decrease in the excretion of allantoin

Perroncito (175) removed the liver only from dogs with Eck's fistula, so that portal stasis did not result The animals excreted urine containing such high concentrations of uric acid that crystals precipitated on cooling Besides the large amount of uric acid excreted, there was marked increase in the uric-acid content of the blood Mann and Magath (126) have reported this same finding following hepatectomy in the dog Perroncito (176) removed the liver from dogs and simultaneously ligated the renal arteries and veins The animals survived from one to four hours after operation, during which

time there was a definite and marked increase in the uric acid content of the blood. Control animals with ligation of the renal arteries and veins as well as ligation of the common and cystic ducts showed no increase in the uric-acid content of the blood. He concluded that the accumulation of uric acid in the blood of hepatectomized animals is due to lack of destruction of uric acid.

Folin, Berglund and Derick (57) published the results of an extensive study of the behavior of uric acid within the body. They attempted to determine the site of destruction of uric acid. They demonstrated that uric acid injected intravenously in the dog was destroyed rapidly, 70 per cent being destroyed the first ten minutes after injection. Excretion of the uric acid by the kidneys is a minor factor in destruction, because only traces of the injected uric acid are found in the urine and the same rapid disappearance of uric acid from the blood takes place even if the kidneys are removed. In the normal dog the renal tissue only seems to be capable of absorbing uric acid injected into the blood stream, since little can be detected in any of the others even if the uric-acid content of the blood is greatly increased. These authors, therefore, concluded that this rapid destruction of uric acid in the dog took place in the circulating blood. Blood from the femoral artery and vein contained the same amount of acid after injection, and no loss of it could be demonstrated in the blood passing through the hind leg of the dog.

In attempting to show that the liver was not the site of uric acid destruction in the dog, uric acid was injected into a dog with Eck fistula, its disappearance from the blood was rapid in this animal also. Further experiments demonstrated that uric acid injected into the portal vein could pass through the liver, since more uric acid was found in the kidneys than in the liver. It was also noted that the uric acid in the heart blood was greatly increased and it was shown that uric acid could be absorbed from the intestine with sufficient rapidity to cause an increase in the uric acid content of the peripheral blood.

The studies on the effect of hepatic poisons on uric acid metabolism have not given the same results. As illustrative of these divergent results and conclusions the following can be cited. Jackson and Pearce (87) noted that the hepatic necrosis which follows the injection

of hematoxic immune serum was accompanied with an increased urinary output of uric acid and purin bases. This result they attributed to the autolysis of necrotic tissue. Wells (222) found that the fatty liver produced by the administration of phosphorus and hydrazine destroyed uric acid as quickly as a normal liver. Williamson and Mann (230) noted that an increase in the uric acid of the blood was a consistent finding after the administration of chloroform and phosphorus.

The relationship of the liver of the dog to uric-acid destruction was demonstrated by the experiments of Bollman, Mann and Magath (16). They performed two series of experiments. In one series, following removal of the liver from a large number of dogs the accumulation of uric acid in the blood was noted, and the amount in the urine determined at intervals corresponding usually to the periods between the taking of blood samples. Other animals were nephrectomized at the time of hepatectomy and the uric-acid content of the blood noted. Because they wished to obtain results for a period longer than a few hours, glucose was administered intravenously to most of the animals. In a few instances it was given by stomach tube, rectally, or by jejunostomy, and in some by combinations of these methods. Fifty per cent glucose was given as a routine, except in cases in which more fluid was desirable for promoting diuresis.

In another series of hepatectomized animals, uric acid was injected intravenously and its content in the blood and urine determined as in the hepatectomized animals to which no uric acid had been given. In a small number of this group the distribution of uric acid to the muscles was studied by removal under local anesthesia, of portions of muscle from an undisturbed site at varying intervals after injection. Control animals for both series were similarly treated except that various surgical procedures were substituted for hepatectomy.

The increase in the uric-acid content of the blood following removal of the liver is striking, a definite rise always occurs within a few minutes and the content remains above normal as long as the animal lives. The course following this initial rise depends on the rate of excretion of uric acid and is approximately inverse to the amount excreted in the urine. In the nephrectomized dehepatized animals the increase in the uric-acid content of the blood begins immediately after opera-

tion and increases gradually at a fairly uniform rate as long as the animal survives. This progressive increase is fairly constant for the different animals and may reach 7 to 9 mgm for each 100 cc of blood at the end of twelve hours after operation. The increase during the first hour appeared to be more rapid than later, but after the first hours, it was proportionate to the length of time after removal of the liver.

The excretion of uric acid in the urine of the dehepatized animal is even more striking than its accumulation in the blood. Unless the volume of urine passed is considerably above normal limits, urate crystals form almost immediately after it is voided and after it has cooled to room temperature about half of the volume is a heavy flocculent precipitate of urates. In general the total amount of uric acid excreted depends on the volume of urine secreted. The total amount of uric acid excreted in the urine by the dehepatized animal is enormous. In all the animals in which there was a free flow of urine for more than twelve hours, the total excretion was at the rate of 1000 to 1500 mgm. in twenty-four hours, with an hourly excretion of approximately 40 to 50 mgm.

When uric acid is injected into a normal dog, very little appears in the urine. When it is injected into a dehepatized dog in amounts which will not injure the kidney but sufficient to prevent a fair flow of urine, 70 to 100 per cent of it can be recovered in the urine. If a standard amount of uric acid for each kilogram of body weight is injected into a normal dog and the rate of its disappearance from the blood noted, it is found within thirty minutes that the uric acid content of the blood has returned to the pre-injection level. When the same amount of uric acid is injected into the dehepatized animal, the content of the blood will be above the pre-injection level at the end of two hours. If the kidneys are removed at the same time as the liver, the uric acid content of the blood remains high after its injection. Estimations of the uric acid of the muscles in such animals demonstrated that the amount injected can be accounted for by the increase of the blood and tissues.

The results of these experiments were all in accord and proved conclusively that the destruction of uric acid in the dog depends on the liver. Since it is evident that uric acid metabolism in the dog and in

man is not the same, it is questionable what part, if any, the liver of man plays in purine metabolism. It has also been shown that bacteria found in the gastro-intestinal tract can form uric acid (MacDonald and Levine (146)). These facts make it difficult to estimate the possible relation of the liver of man to uric acid. However, it should be noted that in some pathologic conditions in which the liver is commonly involved, as eclampsia, there is often an increase in uric acid in the blood or excreted in the urine. Some of this may be due, not to increased production, but to failure of destruction (Plass (178)).

*Creatinin and ammonia* The removal of the liver apparently does not modify in any respect the formation of creatinin (Mann and Magath (131)). The amount of creatinin in the blood of the dehepatized animal depends on the activity of the kidneys. If there is normal excretion of urine the blood creatinin remains the same after removal of the liver as it was before and the amount excreted in the urine is apparently normal. When the kidneys and liver are removed simultaneously, the blood creatinin increases at the same rate as in animals in which only the kidneys are removed.

The absence of the formation of urea in the dehepatized dog cannot be accounted for by an increase in the formation of ammonia (Bollman, Mann and Magath (18)). Following removal of the liver there is a slight increase in the ammonia content of the blood and tissues. There appears to be a marked increase in the excretion of ammonia in the urine immediately after removal of the liver. Usually the ammonia is about three times greater than normal for the first few hours after operation and subsequently decreases. The percentage of the total nitrogen excreted as ammonia is greatly increased, however, because of the marked decrease in the amount of urea nitrogen excreted. Animals in which both kidneys and the liver were removed at the same time, show somewhat greater increases in the ammonia content of the blood. The total amount of ammonia excreted for twenty-four hours by the dehepatized dog is about the same as that excreted by a normal animal, and is much less than that excreted by animals subjected to etherization and laparotomy.

*The constituents of the bile* The particular function of the liver which has thus far been of most importance to clinical medicine is the secretion of bile because of the relation of this product of the liver to



many clinical conditions such as jaundice and disease of the biliary apparatus. The bile is composed of several substances, of which bile salts, cholesterol and bilirubin are considered the most important. One of the most debated questions concerning the action of the liver has been whether it is responsible for elaborating these three important constituents of the bile or whether they are formed elsewhere in the body and merely excreted by the liver. The knowledge in regard to the relation of these two former substances to hepatic function is very incomplete. Little is definitely known about the bile salts either as regards their origin or site of production. Evidence would seem to indicate that they are made in the liver although this has not been definitely proved. Forsgren (60) noted acidophilic granules in the hepatic cells near the periphery of the lobule which he considered indicative of bile acids. Smyth and Whipple (207), from a study of the bile salts excreted in the Eck-fistula animal and after the administration of chloroform concluded that the liver was responsible for making the bile salts. The solution of this problem of the effect of removal of the liver on their formation awaits a satisfactory method of estimating the bile salts in the blood. An advance in this regard has recently been made by Aldrich (2). The knowledge concerning the relation of cholesterol to the liver is very deficient, although apparently no more so than that of the rôle of this substance in the organism as a whole.

Many studies have been made on the origin of cholesterol and its relation to the activity of the liver. McMasters (148) has shown that the output of cholesterol in the bile fluctuates considerably and depends somewhat on the ingested cholesterol. Estimation of cholesterol in the blood before, and at various periods after, removal of the liver does not show any significant changes (Mann (120)). These results do not permit the drawing of conclusions in regard to the relationship of the liver to this substance. Such conclusions might be interpreted as showing that cholesterol is made by the liver and that when the organ is removed no change in the blood content would occur because its utilization is so slow. On the other hand, they might mean that the liver merely excretes cholesterol after it has been made elsewhere in the body but that the rate of its production over its utilization and excretion is too slow to produce a measurable

increase in the blood during the experiments Rosenthal, Licht and Melchior (189) did not determine any consistent effect of removal of the liver on the cholesterol of the blood

The bile pigment is the constituent which has been the subject of the most investigation and discussion of any of the substances excreted by the liver Since the pigment was found in the secretion from the liver it could logically be assumed that it was made in that organ Virchow (220) from results of his studies on the changes occurring in old blood extravasation, raised the question both in regard to the origin of bilirubin from the hemoglobin and the possibility of its being formed outside the liver The first experiments dealing with the effect of removal of the liver on the production of bile pigment outside the liver were inconclusive because the species employed, the frog, does not produce much bile pigment, particularly during the quiescent period, and the methods of detecting this substance were crude at that time

Muller (163) removed the livers of frogs and studied the blood and tissues for the presence of bile pigment He was unable to detect bile pigment in the blood or tissues of frogs that lived four days after the liver had been removed Kunde (102) removed the livers from a large number of frogs, they lived longer than four days, and a green pigment was found in their blood which gave a characteristic reaction He thought this pigment was a precursor of bilirubin, normally excreted by the liver Moleschott (160) kept his frogs alive as long as twenty-one days after the liver had been removed, and could not find pigment in the blood or tissues He believed that the pigment found by Kunde was bile pigment which had been absorbed from the intestine Stern (210) ligated the common duct of frogs and in six weeks could find no trace of bilirubin

The first experimental work which influenced the concept of bile pigment formation and the clinical concept of jaundice was that of Minkowski and Naunyn (158) They removed the livers from hens, ducks, and geese, and subsequently found only small amounts of bile pigment in the urine They believed that the bile pigment found had been excreted into the intestine and later absorbed into the blood They stated that jaundice did not occur in the dehepated animals

of arsenuretted hydrogen, although it was readily produced in the normal fowl McNee (150) repeated the work of Minkowski and Naunyn on geese with similar results. He called attention to the difference in structure of the liver in birds and mammals, and attributed the lack of formation of pigment to the removal of the stellate cells. In the instances in which small amounts of pigment were observed, he concluded that the same type of cells in the spleen and bone marrow were still active. He believed that true hematogenous jaundice in a bird without a liver was impossible. Vogel (221) used ducks and geese and could not obtain any icterus after the removal of the liver and the administration of toluendiamin.

Whipple and Hooper (225), in studying the jaundice that develops in dogs following the injection of hemoglobin, or following chloroform poisoning, found that icterus developed in dogs with Eck fistula similar to that in normal dogs under the same conditions. The decrease in blood supply to the liver did not prevent or delay the occurrence of icterus although it was diminished. The authors concluded that the liver could not be the essential factor in the conversion of hemoglobin to bilirubin. In their next series of experiments they (226) showed that bilirubin could form in the body even when the liver had been removed physiologically. They ligated the hepatic artery in animals with Eck fistulas made previously, injected hemoglobin and obtained a positive test for bilirubin in the blood and in extracts of the fat of some of the animals that lived a few hours following operation. Mann and Magath (126) constantly noted icterus in dogs that survived total removal of the liver for more than six hours. The plasma of these animals became definitely yellow, and the subcutaneous, pericardial and mesenteric fat became a characteristic dirty yellow in contrast to the normal white fat of the dog. Bickel (8), employing the method previously described, removed the livers from dogs and observed the same development of jaundice.

Rich (185), in repeating Whipple and Hooper's work (226), removed the entire abdominal viscera and injected hemoglobin. He was not able to detect bilirubin during or at the conclusion of his experiments although some of his animals lived longer than those of Whipple and Hooper, and he employed a more delicate method for detecting bile pigment. He then repeated Whipple and Hooper's technique, and

found the India ink injected into the external jugular vein or into the aorta, made its way into the liver through small vessels in the diaphragm which enter the liver along the wall of the inferior vena cava. These experiments proved that if an Eck fistula has been made and the hepatic artery ligated the liver may have both arterial and venous circulation although obviously only to a very limited extent. When the blood was also prevented from reaching these small vessels in the diaphragm, the injected ink did not reach the liver. He concluded that the liver was essential for the conversion of circulating hemoglobin to bilirubin.

McNee and Prusik (151) were likewise unable to confirm the results of Whipple and Hooper in the majority of their experiments. They injected hemoglobin in heart-lung preparations and head-thorax preparations and obtained a positive reaction for bilirubin in only a few instances. Makino (117), employing the three-stage method of removal of the liver, noted the development of jaundice in animals in which the liver had been totally removed.

Mann, Bollman and Magath (125) made a thorough study of the pigment which developed in the dehepatized animal. Their experiments were grouped in four series. In the largest series the liver was removed and the development of the pigment followed more or less as a routine, qualitatively and sometimes quantitatively. Most of the experiments were performed primarily for the purpose of observing other effects of the total loss of the liver. In one series of experiments, hemoglobin was injected intravenously after removal of the liver to determine if such injection would hasten the formation of the pigment. In another series the spleen was removed at the same time or previous to the removal of the liver. In a few experiments, a reverse Eck fistula was made and later all the abdominal viscera were removed. In the last series the portal circulation through the liver increased before the liver was removed, in contrast with the other series in which it was abolished.

The results of all the experiments were definite. A specimen of urine obtained from a dehepatized animal a few hours after operation was bile tinged and gave a positive test for bilirubin. In from three to six hours after the liver was removed the plasma becomes tinged with yellow. This color usually increased progressively until death,

and the reaction for bilirubin was positive. A yellow tinge also developed in the sclerotics in the animals that lived sixteen hours or more after operation, and could sometimes be seen in the mucosa of the mouth also. At necropsy all the fatty tissue was dirty yellow. The chloroform extract of this fatty tissue was yellow and gave a positive reaction for bilirubin. The yellow pigment, wherever found, was positive for bilirubin by all the more satisfactory tests, although the van den Bergh test was most reliable. This test is at first indirect and toward the end of an experiment may become biphasic. The removal of the spleen either at the same time or previous to the removal of the liver, in no way affected the development of the pigment. The pigment also developed when there was no blood present in any of the serous cavities.

Four possible modes of origin for the pigment were considered: squeezing from the liver at the time of operation, absorption from the bile present in the intestine previous to operation, storage in some organ previous to operation, or production by some tissue. That it was not squeezed from the liver at the time of operation was proved by the facts that it was not found in the plasma immediately after operation, that it increased progressively, and the careful clamping of the vena cava before removal of the liver did not prevent its occurrence. That it was not absorbed from bile in the intestine, which had been discharged previous to operation, was proved by the fact that removal of the gastro-intestinal tract at the time of removal of the liver did not prevent its occurrence. That it had not been stored in some organ previous to operation is evident, since the amount in the urine and the amount found in the blood and tissues at death was too large to have been stored in any one organ or tissue without giving evidence of its existence. It was thus necessary to conclude that the pigment had been formed in some extra-abdominal organ or tissue.

Melchior, Rosenthal and Licht (155) studied the development of bile pigment following removal of the liver and following the injection of toluendiamin into normal and dehepatized dogs. They removed the liver from dogs, employing the three-stage method, and observed the appearance and accumulation of a yellow pigment in the urine, plasma, and fat which had been previously observed by others. However, while this pigment gave a positive van den Bergh test for biliru-

bin, they concluded that, since the yellow of the plasma appeared to develop faster than the color of the van den Bergh test, most of the yellow coloration of the plasma and fat of the dehepatized animal was due to a pigment other than bilirubin. No evidence of the nature of the other pigment was obtained. They also studied the effect of removal of the liver in animals jaundiced by the previous administration of toluendiamin. If the liver was removed in a dog which was jaundiced by toluendiamin, the bilirubin content of the plasma not only stopped increasing but actually decreased. From the results of their experiments they conclude that, while bilirubin appears in the plasma of the dehepatized dog and while it can be found extrahepatically, the amount is insignificant and the liver is essential for the development of a real jaundice.

Kallo (93) studied the effect of the injection of glucose in animals poisoned with toluendiamin and observed a diminution of the jaundice. Rosenthal, Licht and Melchior (189) found that the jaundice which follows the administration of phenylhydrazin was almost prevented by removal of the liver.

While the yellow pigment which appeared in the urine, plasma, and tissues of totally dehepatized dogs gave a positive reaction to all the accepted chemical tests for bilirubin, the objection could be made that it might not be bile pigment because the chemical tests for bilirubin are not considered absolutely specific. However, the final evidence that this pigment which develops in the dehepatized animal is bilirubin and that it does form extrahepatically was furnished by certain experiments made by Mann, Sheard, and Bollman (134), in which the spectrophotometric method was introduced as a method of precision in identifying and estimating bilirubin. The principles of the spectrophotometer, the method of employing it, and the criteria necessary for interpreting the results and the method of preparing the solutions for examination can best be obtained from the published report of Sheard, Baldes, Mann, and Bollman (205). It is sufficient to note here that with the spectrophotometric method, properly employed, it is possible to identify and measure accurately a minute amount of bilirubin, that is, an amount approximately one-fifteenth of the smallest amount measurable by the van den Bergh (5) method.

Three series of experiments were performed. In one series the

common bile duct was ligated and the gallbladder removed. Mann and Bollman (123) demonstrated that by this procedure a positive test by the van den Bergh could be obtained within a few hours. In another series the liver was totally removed and in the third series all the intra-abdominal viscera were removed.

As determined by the spectrophotometer, the curves of light transmission of the pigment which appeared in the plasma of dehepatized dogs, of the dogs with all intra-abdominal viscera removed, of the dogs with obstructed common bile duct and gallbladder removed, and of the pigment in the bile obtained from the gallbladder were identical in nature.

Rich (186) removed all the intra-abdominal organs of dogs after previously ligating the vena cava and forcing a collateral circulation to develop, and was able to demonstrate the presence of bilirubin in the plasma.

Mann, Sheard, and Bollman and Baldes (137) proved that some bilirubin is made in the liver. This was accomplished by estimating by the spectrophotometric method, the amount of bilirubin of the blood entering the liver and the amount leaving it after removal of the spleen and gallbladder, and ligating the common bile duct. It was found that the blood leaving the organ contained slightly more bilirubin than the blood entering it. On the other hand, the same investigators found that the amount of bilirubin formed in the liver was insignificant as compared with that formed in the remaining portion of the body. If the gallbladder was removed and the common bile duct ligated, the bilirubinemia, as determined by the spectrophotometric method, began immediately and for the first few hours increased at a constant rate. The routine procedures of the experiment were (1) to secure a specimen of arterial blood for estimating the normal bilirubin content, (2) to remove the gallbladder and obstruct the common bile duct, (3) to secure specimens of arterial blood every fifteen minutes for an hour or hour and a half, for determining the rate of development of the bilirubin, and (4) removing the liver when a sufficient number of bilirubin estimations had been secured to determine the curve of bilirubinemia. The results of these experiments showed that little or no effect was produced by the removal of the liver. This proved that in the normal animal the amount of bilirubin

made in the liver was insignificant. Other investigations (Mann, Sheard, Bollman and Baldes (136)) proved that most of the bilirubin of the normal animal is formed in the bone marrow.

*Detoxicating action of the liver* One of the most popularly ascribed functions of the liver is that of a detoxication, meaning a specific function of making toxic substances harmless to the rest of the body. Several of the so-called tests of hepatic function are based on this supposed function. Much of the experimental work presented as evidence to substantiate this hypothesis consisted in comparing the specific reaction of a known substance when injected into the portal vein and a systemic vein. It can often be demonstrated that much less general reaction is produced when the injection is made into the portal vein. It has thus been inferred that the liver has detoxified the substance injected. It would appear obvious that the control injection should be made to pass through a capillary bed before reaching the general circulation in order to make a comparison with the effect of the injection into the portal vein. This appears to have been done rarely (Koessler and Hanke (99)).

Whether or not the liver is considered as a specific detoxifying organ will depend somewhat on what is meant by detoxifying activity. If the protective function of the organ is considered in the light of its relation to various phases of metabolism, as previously discussed, a detoxifying activity can be ascribed to it. If the action of the hepatic poisons is considered as due to the liver removing them from the blood in order to prevent injury to the rest of the body and the liver itself being injured thereby, it would represent a detoxifying function of the liver. If the activity of the liver, probably mainly a function of the stellate cells, in removing foreign particles from the blood stream (Drinker and Shaw (38)), (Drinker, Shaw, and Drinker (39)), in participating in immunity and anaphylaxis as reviewed by Gunn (73) and Opie (169) is considered as detoxifying function, the liver is a true detoxifying organ.

It should also be noted, as found by Flexner and Sweet (53) in regard to dysentery toxin, mercury and ricin, that the liver excretes poisons in the bile. Probably many of the heavy metals are eliminated from the blood stream in this manner.

Pelkan and Whipple (174) found that when the liver was injured by



chloroform or following an Eck fistula, there was a reduction in the rate of conjugation of phenol, and Delprat and Whipple (33) found that following similar hepatic injury the synthesis of hippuric acid from benzoate was retarded. However, the dehepatized animal does not appear to be greatly hampered in the conjugation of either of these substances (Mann and Bollman (124)). The rate of the conjugation of phenol injected into the blood of a dehepatized animal is little altered from that of normal animals, the free phenol in the blood rapidly returns to normal, and there is an increase in the amount of conjugated phenol in the blood. Synthesis of hippuric acid also occurs in the animal after removal of the liver following the injection of sodium benzoate.

The dehepatized animal is not capable of withstanding the injection of amounts of certain substances as phenol, benzoic acid, phenol-tetrachlorophthalein and several others as the normal animal. The injection of an amount of such substances which will produce little or no reaction in the animal before removal of the liver may prove fatal after the liver has been removed (Mann and Bollman (124)).

It is thus seen that in many ways the liver does protect the body from injurious agents, but how it does this is not known. It is probably not correct however, to ascribe to the liver an important specific detoxifying function.

*Cellular elements of the blood and fibrinogen* The liver is a part of the hematopoietic system of the fetus and appears to retain an intimate relationship to the blood in the adult. Whipple (224) has shown that it is an important storehouse for the material from which hemoglobin is made, and Lamson (103) has demonstrated that it may be of importance in storing red cells in the adult. The dehepatized animal does not show any changes in hemoglobin or red cells that cannot be accounted for by the effect of operation, glucose injection, and so forth, (Mann, Bollman, and Magath (125)). This is about what might be expected when the length of the experiment is considered, and does not detract from the value of the other experimental investigations of hepatic functions of this nature.

The liver has also been considered as being of great importance in the formation of the plasma proteins and in this respect the work on the formation of fibrinogen is of the most interest. However, since

most of the work which appears to show relation between hepatic activity and the formation of fibrinogen was done on animals in which the liver was injured with one or another of the hepatic poisons and very few experiments were performed on the totally dehepatized animal, a review of the results of both methods of investigation will be given. Corn and Ansiaux (30) studied the changes in coagulability of the blood in phosphorus poisoning and determined that it was due to the decrease of fibrinogen. Jacoby (89) corroborated the data of these observers. Doyon, Morel and Kareff (37) associated this decrease of fibrinogen in phosphorus poisoning to the toxic action of the substance on the liver. Doyon (34) showed the same relationship of the decrease in fibrinogen to hepatic injury by chloroform. Whipple and Hurwitz (228) studied the effect of chloroform anesthesia on the liver and the changes in fibrinogen content of the blood. They noted a decrease in the fibrinogen during the acute stages of hepatic injury and a return of the fibrinogen to the normal value as hepatic regeneration occurred. Meek (152) studied the regeneration of fibrinogen after defibrinogenation in animals in which the liver had been functionally removed by making an Eck fistula and ligating its blood supply. He did not find regeneration occurring after exclusion of the liver. Williamson, Heck, and Mann (229) studied regeneration of fibrinogen in the dehepatized animal but were not able to draw any definite conclusions. A decrease in fibrinogen has also been noted in hepatic disease (Isaac-Krieger and Hiege (85), McLester and Davidson (147)). Foster and Whipple (62) estimated the fibrinogen of the blood under normal conditions following various diets and after different procedures which included hepatic injury, shunting of the portal blood from the liver, and so forth. They noted a decrease in the fibrinogen associated with the hepatic injury and restoration to normal as hepatic repair occurred. Schultz, Hall, and Baker (202) produced extensive infarct-like lesions in the liver of dogs by injecting small doses of chloroform into the portal system and noted the repair of these lesions. There was a prolonged clotting time of the blood in many of the animals a day or two after the chloroform had been administered. Some of the animals died from hemorrhage. Bleeding occurred not only into the peritoneal cavity but externally. However, in the later stages of hepatic repair, three or four weeks after the lesions were

induced, and when hyperplasia and hypertrophy of the liver were usually marked, the blood appeared to clot with extraordinary rapidity. Schultz, Nicholes, and Schaefer (203) studied the effect of chloroform injection into the portal system, chloroform anesthesia and the administration of carbon tetrachloride by mouth on the fibrinogen content of the blood. They found that all three of these procedures produced a decrease in fibrinogen which returned to its normal level. The rate of return to normal depended on the degree of hepatic injury. Slight injury produced an immediate rise in the fibrinogen. Rosenthal, Licht, and Melchior (189) noted an almost complete disappearance of fibrinogen about fourteen hours after removal of the liver.

In this connection, it should be noted that some observers have found evidence of extrahepatic formation of fibrinogen. Brown-Séquard (21) concluded it is formed in the intestines. According to Dastré (32) not only the intestine but also the lungs and skin are sites of fibrinogen formation. Mathews (243) concluded it is formed in the intestine. According to Goodpasture (67) the intestine is important in fibrinogen formation. Other observers (Muller (164)), (Morawitz and Rehn (161)), concluded it is formed in bone marrow or by leukocytes.

A review of the evidence regarding the site of formation of fibrinogen indicates that it has not been definitely proved that the liver is alone responsible for its formation, although most of the evidence would seem to show that hepatic activity is of great importance. Some of the reasons why the evidences are contradictory are: (1) the difficulty of obtaining accurate estimates of fibrinogen; while several promising methods of estimating fibrinogen have been developed, an analysis of the results obtained would seem to indicate that they are not wholly satisfactory, (2) the fibrinogen content of the blood appears to fluctuate for many reasons, this makes it difficult to analyze the results of removal of the liver, in which the anesthetic, loss of blood, peritoneal irritation and other complicating factors are present. However, it has been shown that injury of the liver or its removal affects the formation of a normal blood clot and the most logical conclusion is that this result is produced by a failure of the formation of fibrinogen. On the other hand the possibility must be recognized that the failure to form a normal blood clot may be related to the character of fibrinogen or to some other element necessary for the formation of fibrin.

## THE EFFECT OF PARTIAL REMOVAL OF THE LIVER

It is logical to assume that the most important investigations of the liver from the clinical standpoint are those in which pathologic conditions similar to those found in man could be produced experimentally for intensive study. Many such investigations have been performed and data of sufficient value secured to warrant conclusions. However, it is difficult to evaluate data obtained by a study of pathologic conditions produced experimentally in terms of hepatic functions, and therefore, the definitely established facts determined by a study of the dehepatized animal are of inestimable value to use as a standard.

*The regenerative power of the liver* The greatest difficulty encountered in the experimental production of permanent reduction of hepatic function by injury to, or partial removal of, the organ is its high restorative power. Injury by any of the hepatic poisons not sufficient to produce death, is usually quickly recovered from and permanent damage is often not great. This power of restoration is made even more noticeable by the results of partial removal of the organ. This was observed originally by Ponfick (180) and also by von Meister (154), Flock (54), Mann and Bollman, and others, while a complete study has been made by Fishback (47). It has not been found possible permanently to reduce a substantial amount of hepatic tissue of the normal dog. In the dog the various lobes of the liver stand out separately so that it is anatomically possible to remove it lobe by lobe. Although it is possible to remove or leave any lobe or combination of lobes, it is necessary to leave whole lobes, partial removal of a lobe is attended with grave damage from hemorrhage or from destruction of the vascular radicles to the portion remaining. The maximal amount of hepatic tissue that can safely be removed from a dog is limited to certain combinations of lobes, which may rarely exceed 70 per cent of the total amount of hepatic tissue. If as much of the liver is removed from a normal animal as is anatomically possible, the remaining tissue will increase and in a few weeks reach approximately the preoperative amount. As new lobes do not form and the return to normal size is by an increase in remaining lobes, it is impossible to remove a significant portion of the restored organ. This great restorative power of the liver, together with the anatomic limitation

of removal prevents the permanent reduction of hepatic tissue in the normal animal and definitely precludes the employment of this method for the production of hepatic insufficiency

*Methods of reducing hepatic function* In general three methods have been employed to reduce hepatic tissue in an endeavor to reduce hepatic function (1) the use of hepatic poisons, (2) ligation of some of the various radicles going to a lobe of the liver or reduction of the blood supply to the whole organ, and (3) the removal of various amounts of hepatic tissue after diversion of the portal blood from the liver

Probably more experimental work has been done to produce and study reduction of hepatic function by the use of the hepatic poisons than by all other methods. Some of these investigations have been noted herein when the results were pertinent to the subject being discussed. Very little more of value can be added. These investigations have been of considerable value in regard to hepatic physiology although in many instances the results have been either inconclusive or contradictory. One of the most important facts determined was the great regenerative power of the liver after injury. It has been considered of such significance as to constitute, in the opinion of some of the investigators, the most important result obtained (Pearce and Jackson (172)). The possible sources of error in the method have sometimes been clearly recognized, as illustrated by the statement of Marshall and Rowntree (141), that deductions concerning hepatic function drawn from studies of hepatic poisons are not free from criticism and may be applied to clinical medicine only with reserve, although often this conservative attitude has not prevailed.

There are many factors which make it difficult to draw positive conclusions relative to hepatic function from the results of the administration of hepatic poisons. Among these may be mentioned (1) other organs besides the liver are often badly injured, (2) the study of the constituents of the blood and urine is complicated by the products of cell autolysis produced by the direct action of the poisons, and (3) the impossibility of standardizing all the conditions of the experiments. These complicating factors probably account for most of the divergent results secured. However, with increased knowledge of the functions of the liver and methods of standardizing experi-

mental conditions, important advances in experimental production of pathologic conditions of the liver together with a better understanding of the development of such pathologic processes, their diagnosis and possible prevention, may be obtained by the use of the various hepatic poisons. A few illustrations follow.

Whipple (223) found that pups, during the first three weeks of life, were resistant to chloroform. Graham (70) concluded that this resistance was due to the high content of hepatic glycogen in pups. Opie and Alford (170) found that a carbohydrate diet protected the hepatic cells from both chloroform and phosphorus and that chloroform produced its maximal effect with a diet of fat and phosphorus or a diet of protein. All these investigations were performed before the value of an adequate diet and the length of time necessary to obtain results on a particular diet were recognized. Moise and Smith (159) have repeated these experiments, using a maintenance diet high in one of the various foodstuffs given over a sufficient length of time. They found that while a high carbohydrate diet protected the hepatic cell and that a high fat diet afforded the least protection, the high protein diet was of the greatest value in preventing hepatic damage. Lamson and Wing (104) found that carbon tetrachloride produced characteristic and marked cirrhosis of the liver. Lewis and Izume (86, 108) found in carefully conducted experiments and carefully analyzed data that the results of administration of hydrazin are quite comparable, in regard to nitrogenous metabolism and hypoglycemia, to removal of the liver. Such researches give promise of being of much value to clinical medicine.

Any one of the three vascular radicles going to a lobe of the liver can be ligated with safety but ligation of any two of these radicles usually soon causes the animal's death. In some animals, as the rabbit, ligation of the branch of the hepatic artery to a lobe produces atrophy of the lobe with proliferation of the contained bile ducts (Janson (91)). Ligation of the portal radicle produces atrophy of the lobe involved. Ligation of the duct radicle also produced atrophy and a certain degree of cirrhosis. Employing the two latter procedures of reducing hepatic tissue, Rous and Larimore (191) made some important contributions to hepatic physiology. They found that the degree of atrophy depended on several factors, the most important of

which was in relation to the hypertrophy of the remaining portion of the liver. If this portion was left intact, it hypertrophied while the lobe in which the portal or duct radicle had been ligated atrophied. However, if the portal radicle to one lobe was ligated and the duct radicle to another, this extreme degree of atrophy did not occur. The method appears to have limitations from the standpoint of permanently reducing the hepatic tissue to an insufficient level.

In connection with the discussion of ligating the various vascular radicles of the liver, it might be well to note that the production of an Eck fistula is the most common method of decreasing the blood supply to the liver. Whenever the results of studies on the Eck fistula have been pertinent they have been considered with those on the dehepated animal. It is not feasible to include a general consideration of the Eck fistula animal. While there is sufficient evidence to conclude that the diversion of the portal blood produces a definite and marked decrease in hepatic function, as previously stated this decrease is probably not sufficient to warrant the large number of investigations which have been made on the Eck fistula animal.

A method of producing a permanent decrease of hepatic tissue in the dog by removal of various amounts of liver after an Eck fistula has been made has been reported by Mann and Magath (127) and physiologic studies on such animals have been made by Mann and Bollman (124). It was found that the ability of the liver to restore itself after partial removal depended for the most part on an intact portal circulation. When the portal circulation is shunted from the liver as occurs following an Eck-fistula operation, the liver undergoes more or less characteristic atrophy (Whipple and Hooper (227)). If, after a certain degree of atrophy has occurred and a portion of the liver is removed, little or no effort is made to restore the organ to its preoperative size. It has thus been possible to reduce permanently the amount of hepatic tissue. The routine of the procedure is as follows:

An Eck fistula is performed, thus shunting the portal blood from the liver. After sufficient time has elapsed for the liver to atrophy somewhat (not more than two months) various lobes or combinations of lobes are removed. Approximately 60 per cent, and occasionally a slightly larger percentage, of the organ can be removed in the Eck fistula animal, as the liver has usually decreased from a fourth to half

following the Eck fistula, the amount remaining may be less than 20 per cent of the original tissue. Also, since the amount remaining is greatly affected by the loss of portal blood, and since in many instances only a few hepatic cells in each lobule appear normal, the functional capacity of the organ is markedly and permanently decreased.

An intensive study was made by Mann and Bollman (124) on dogs in which the hepatic tissue had become permanently reduced to only a small percentage of the normal amount. Those physiologic processes which are capable of being determined quantitatively and which are so constantly and definitely affected by the total removal of the liver were studied particularly. In many of the experiments, observations were made and data secured by the use of standardized procedures in the normal animal, in the same animal after an Eck fistula had been made, and again at various periods after the removal of different amounts of the liver. In some instances the observations extended over more than two years and the amount of liver remaining at the end of the experiment was estimated as less than fifteen per cent of the normal. These experiments demonstrated that the liver not only has enormous restorative power but also enormous ability for physiologic compensation.

Since certain phases of carbohydrate metabolism were so strikingly affected by total removal of the liver, it would seem that greatly decreasing the amount of tissue would produce demonstrable and measurable changes in these same processes, but this was not found to occur in a comparable degree. For instance, the blood-sugar level which is so constantly and profoundly affected by total removal of the liver is but slightly changed by the reduction of tissue to only a small percentage of the normal.

The blood-sugar level of the normal dog under standard laboratory conditions in reference to training for the necessary procedures of obtaining blood samples and for the fasting before observation, and so forth, undergoes only slight fluctuation from hour to hour and day to day. This gives a fairly uniform standard by which to compare the blood-sugar level of animals in which the functional capacity of the liver has been decreased. Certain observations of a positive nature stand out. The fasting blood-sugar level of the animal with Eck fistula is usually slightly lower than that of a normal animal.



When part of the liver of an animal with Eck fistula is removed surgically, the blood-sugar level is usually slightly decreased, as compared with the level before operation. However, it is possible to detect this decrease in the blood sugar level in the condition of reduced hepatic tissue only by careful control of laboratory conditions. Furthermore, while the level of blood sugar decreased in animals with reduced hepatic tissues, a level was finally reached at which the blood sugar remained constant, regardless of the further decrease in hepatic tissue. These experiments prove that the liver stubbornly maintains an adequate blood-sugar level even though greatly incapacitated by the loss of much of its substance.

One of the most interesting observations made on the significance of reduced hepatic tissue on the blood-sugar level was recorded by Mann and Magath (130). They found that if an appropriate amount of hepatic tissue was removed from an animal with Eck fistula at the same time the pancreas was removed, the characteristic hyperglycemia that always follows the latter procedure in the normal animal did not occur, or only to a slight degree, although the other signs of pancreatic diabetes appeared. As a corollary to these experiments are those in which the effect of a standard amount of insulin was determined before and after partial hepatectomy in an Eck-fistula animal. It was found that whereas the blood-sugar level recovered readily following the injection of a small amount of insulin, when a considerable portion of the liver was removed the rate of recovery of the blood-sugar level was greatly prolonged (Mann and Magath (133)).

As previously noted, experiments dealing with total removal of the liver demonstrated that transitory hyperglycemia does not occur in dehepatized animals. Experiments on animals with Eck fistula and also with greatly reduced hepatic tissue have demonstrated that some of this transitory hyperglycemia depends for the most part on an intact portal circulation. An increase in the blood sugar either does not occur or occurs only to a slight extent in animals with Eck fistula following etherization and operation. On the other hand, an increase in blood sugar can be produced in such animals by the injection of epinephrin, although a larger amount of epinephrin appears necessary and the amount of hyperglycemia produced appears to be considerably less than in animals with normal livers, under the same conditions as regards diet and so forth.

The results of the studies on the detoxicating action of the liver in the animals with greatly reduced hepatic tissue were comparable to those on the dehepatized animal. The injection of many substances in amounts which in the normal animal would be tolerated without producing symptoms, would prove serious to the animal with greatly reduced hepatic tissue and might cause death. On the other hand evidence was not obtained that the normal animal acutally destroyed these substances better than the animal with reduced hepatic tissue.

Although urea formation in the body depends entirely on the presence of the liver, since there is no formation of urea in the dehepatized animal, it was not possible to demonstrate any decrease in the formation of urea even in those animals with the lease hepatic tissue. The total amount of urea nitrogen in the urine of fasting animals is approximately the same whether they are normal or have been subjected to an Eck fistula, or have been deprived of most of their hepatic tissue. The amount of urinary urea is increased by increases in the protein content of the diet. The ingestion of milk by such dogs produces an excretion of urea in the following twenty-four hours which is almost identical with that of a normal animal on the same diet. The ingestion of meat also failed to bring out any difference in the excretion of urea which could be attributed to differences in the amount of hepatic tissue in the animals observed. There was evident diminution, however, of the percentage of the total nitrogen excieted as urea by the Eck fistula animals, but subsequent removal of the major portion of the liver failed to produce any further reduction of the urea percentage. This reduction is produced largely by an increase in the excretion of ammonia, which is probably not directly attributable to hepatic injury, since similar changes may be produced by any condition which alters the acid-base equilibrium of the body toward the acid reaction.

The cessation of urea formation in the dog whose liver has been removed allows the accumulation of increased amounts of amino acids in the blood, urine, and tissues. Since the greater part of this amino-acid nitrogen is absorbed by the muscles and only a minor part is found in the blood and urine, it is not surprising that studies of the amino acid content of the blood and urine have not shown great changes due to partial removal of the liver. This fact may also have considerable bearing on the amount of amino acid in the blood and

urine in disease No significant quantitative changes in the amino-acid nitrogen of the blood were found even in the animals with the least hepatic tissue, and the amount of amino-acid nitrogen excreted in their urine was but slightly greater than that of normal animals The use of diets of moderate or excessive content of protein also failed to bring out any great differences The same may be said for the intravenous injection of glycocoll or alanin, since these amino acids remain in the blood and appear in the urine in only slightly greater amounts after a large amount of hepatic tissue has been removed It is noticeable, however, that the tolerance for intravenous injections of alanin or glycocoll is greatly diminished by a reduction in the amount of hepatic tissue. The injection of amounts of amino acids that are without visible effect in a normal animal produces cardiac irregularity, increased respiration and often collapse if the amount of hepatic tissue has been greatly reduced The dehepatized dog will not survive the rapid injection of large amounts of amino acids which do not produce symptoms in the normal animal

As previously noted uric acid is not destroyed in the dehepatized dog The destruction of this substance in the normal dog seems to be entirely dependent on the presence of the liver since it is not destroyed in the absence of the liver and no other means of influencing its destruction has been demonstrated Following the intravenous injection of uric acid in the normal dog, there is rapid disappearance of the excess uric acid in the blood and only a very small increase in the uric acid in the urine. When the same amount of uric acid is injected into a dog with Eck fistula, the disappearance of the uric acid is somewhat delayed and a slight increase in its excretion occurs Further reduction of the amount of hepatic tissue causes greater delay in the disappearance from the blood of the injected uric acid and the excretion in the urine is increased The reduction in the rate of disappearance and the amount appearing in the urine are greater the greater the reduction in the amount of hepatic tissue

Studies on the uric acid in the blood and urine have been most satisfactory in showing increase in uric acid roughly proportional to the extent of the reduction of hepatic tissue Normal dogs have but a trace of uric acid in the blood and excrete but a trace in the urine Following the institution of an Eck fistula, there is a tendency toward

a higher level of uric acid in the blood under fasting conditions, and the amount of uric acid in the urine is greatly increased. After further reduction of hepatic tissue, the uric acid of the blood increases, and may contain as much as ten times the normal amount for a few weeks after removal of the major portion of the liver. Any further increase in the uric acid of the blood has invariably been attended by the decline and death of the animal. At necropsy the liver is shown to have been reduced by operation or to have atrophied to a minimal amount. The amount of uric acid in the urine of the fasting animal is also increased by reduction in the amount of the hepatic tissue. Under ordinary dietary conditions the amount of uric acid in the urine is increased over the fasting level, and a greater increase appears with the greater reduction in the amount of hepatic tissue.

With a high purin diet the uric acid excretion of normal dogs may be increased to an appreciable amount and is quite constant for a given diet. Eck fistula dogs, on the same diet, excrete from two to four times the normal amount of uric acid, and it has been observed at operation and at necropsy that the liver is more atrophic. The removal of portions of the liver from these animals gives rise to a greater excretion of uric acid in the urine when they are subjected to this same diet. Sweet and Levene (212) also noted an increase in excretion of uric acid in Eck-fistula dogs after a feeding of nucleoproteins.

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## NON-SPECIFIC THERAPY

JOSEPH L. MILLER

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Non-specific therapy has been utilized as protein therapy chiefly in acute and chronic infections. More recently non-specific desensitization has interested both the clinician and laboratory worker. Still more recently attention has been drawn to a possible non-specific factor in chemotherapy. These three topics, therefore, enter into the discussion.

### PROTEIN THERAPY

The quite independent investigations of Kraus and Mazza (1) and Ichikawa (2), both reported in 1914, were responsible for stimulating interest in this subject. This interest has been maintained and a very extensive literature, largely of German origin, has accrued.

Ichikawa treated typhoid with intravenous typhoid vaccine. He observed that he was not only able to reduce the mortality, but greatly to shorten the course of the disease. Many cases terminated by crisis following a single treatment, others recovered after rapid lysis, while in other cases the course of the disease was not modified. He then treated paratyphoid patients with typhoid vaccine with equally good results, thus demonstrating that the treatment was not strictly specific.

Kraus and Mazza went one step further, using colon bacillus vaccine. They demonstrated that it was just as efficient as specific vaccine. They later used colon vaccine more or less successfully in the treatment of puerperal sepsis.

Soon after this, Ludke (3) demonstrated that bacterial vaccines were not essential, as equally good results could be obtained with the intravenous injection of albumose. Later, Schmidt (4) and Saxl (5) discovered that milk injected intramuscularly would serve the same purpose. Since then a multitude of agents have been used, many of



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them proprietary Whether any one of them is more efficient than typhoid vaccine has not been proved They all have one point in common, the ability to cause a febrile reaction

A review of the literature, however, reveals that many years previous to the work of the above mentioned investigators, clinicians had reported recoveries which we now account for on the basis of protein therapy

Rumpf (6), in 1893, treated typhoid with pyocyaneus vaccine subcutaneously Following the injection there was a rise in temperature and the course of the disease was frequently definitely modified Horbaczenski shortly before this reported good results in lupus vulgaris following nuclein injection Somewhat later, Vaughan reported on the value of nuclein in tuberculosis

Colloidal metals first introduced by Credé with the idea that their action was specific, owed their beneficial action to non-specific agencies

Coley's fluid, employed in the treatment of malignant growths, was not specific, as any agent capable of producing a violent temperature reaction would probably yield the same result

Hiss and Zinsser's (7) leucocyte extracts probably owed their therapeutic effect to a non-specific reaction

Mysterious, prompt subsidence of typhoid following blood transfusion or intravenous normal salt solutions in case a chill occurred, can now be explained on a non-specific basis

It is unnecessary to enumerate the various non-specific agents that have been used during the past ten years Some of these were introduced and are still considered by some as possessing specific characters. A few may be enumerated bacterial vaccines, bacterial extracts, as tuberculin, normal blood serum of man and various lower animals, milk, casein, gelatin, proteoses, both plant and animal, Witte's peptone, colloidal metals, mercurochrome, and malaria and relapsing fever inoculation

To those interested in protein therapy it is more important to select one agent and become familiar with the dosage and degree of reaction desired than it is to try various agents, with the idea that some are of special value in certain diseases In the past the writer has used a considerable number of highly lauded preparations, lured by the glowing reports of their value, but has always returned to typhoid vaccine.

All agents used for this purpose excite a temperature reaction. There may be only a moderate rise in temperature or more frequently an actual chill. Whether good results can be obtained without a distinct temperature reaction is still a debatable question. The writer has tried a considerable number of agents reported to give results without temperature reaction, but in his hands they have all failed, at least the results were not noticeably beneficial, in fact, the degree of reaction bears some relation to the efficiency of the treatment. When repeated moderate or good reactions have given only temporary benefit, a larger dose with very severe reaction may effect a permanent cure. Severe reactions are to be avoided, as they are not free from danger. Nevertheless, our experience indicates that the more severe the reaction the greater the chances of relief. This is not to be interpreted as a suggestion to give excessive doses. Our experience with extreme reactions has been acquired largely through a mistake in measuring the dosage. It is not improbable that the good results obtained with mercurochrome may be due to the violence of the reaction, as the writer has rarely noted such severe reactions after typhoid vaccine as have been observed after mercurochrome.

The reaction in chronic infection, as chronic arthritis, following a moderate dose of typhoid vaccine (twenty-five million) appears in one-half to one hour. There is either marked chilliness or an actual rigor, with general aching like that observed at the onset of any acute infection. Occasionally there is vomiting. Not infrequently within six to twenty-four hours there may be a second chill. Some cultures are very prone to give recurrent chills. The inconvenience experienced by the patient is not greater than occurs with the initial chill of an acute infection and not necessarily more dangerous. There is a marked difference with which individual patients react to the same dosage. In the writer's experience it is impossible to determine just the dosage that will always give a good reaction.

In acute infections, as typhoid or pneumonia, the dosage should be reduced. Even with very moderate doses the temperature may reach 105° to 106°F. We have seen temperatures of 108°F in pneumonia following an injection of twenty-five million typhoid bacilli, but have



never observed serious consequences Profuse perspiration gradually reduces the temperature to normal or subnormal Occasionally a degree or more of temperature may persist for one or two days

The increase in pulse rate conforms to what occurs in fever of the same degree from other causes There may be marked cyanosis during the chill, not more marked however than may be noted in the initial chill of an acute infection, in fact, the reaction is of the same character.

It is difficult to take the blood pressure during a chill We have been able to demonstrate a rise in systolic pressure of 25 to 30 mm As the temperature returns to normal or subnormal there is a corresponding fall in blood pressure

Immediately following the injection there is a leucopenia due to reduction of the polynuclear cells With the onset of the chill there develops a gradually increasing leucocytosis which reaches the maximum in four to nine hours, gradually returning to the previous level within twenty-four hours The leucocytosis is of the polynuclear type Occasionally, as reported by Cowie and Calhoun (8), abnormal cells appear in the blood, as myelocytes, normoblasts and megakaryoblasts In previously afebrile patients the average leucocytosis varies from about 13,000 to 15,000 In acute infections, as pneumonia, it may reach 40,000 to 50,000 In a series of fifteen pneumonias treated with typhoid vaccine we were unable to establish any relationship between the degree of leucocytosis and the beneficial results

Several observers have called attention to the marked hyperglycemia without glycosuria following the reaction In one patient with chronic arthritis the blood sugar reached 350 mgm per 100 cc of blood without glycosuria

The reaction is thought to modify vascular permeability However, this point is not settled Siegert (9) and Schmidt (10) have reported increased permeability following moderate reaction Starkenstein (11), on the other hand, reported lessened permeability

Davis and Petersen (12) found an increased lymph flow in dogs immediately after the injection which persisted for several hours The opinion has been expressed that this favors the distribution of antibodies and may be a factor in immunization Assuming that an increase of antibodies in the blood is responsible for the immunity follow-

ing protein therapy, the question arises whether this is due to increased antibody formation or increased mobilization of preformed antibodies. When increased antibodies are found in the blood it is difficult or impossible to determine whether their presence is due to increased formation or increased mobilization.

Hektoen (13) observed that rabbits sensitized to horse serum produced anti-horse precipitin when injected with another serum.

Bieling (14), in rabbits immunized to typhoid bacilli, was able to demonstrate increased typhoid agglutins after injecting colon, dysentery or diphtheria bacilli.

Flechseder (15), following injection of albumose in typhoid, and Parlavecchio (16), with nuclein, were able to demonstrate increased agglutins.

Culver (17) studied the serum in sixteen cases of gonorrheal arthritis following injection of proteose. He decided that both primary and secondary proteoses increased either the antibody formation or mobilization to the same degree as specific vaccine. Jobling, Petersen and Eggstein (18) found increase in proteolytic enzymes and lipases in laboratory animals following the injection of various non-specific agents.

Ling (19) recently reported that natural immune bodies, including bacteriolysins, were mobilized or at least appeared in the blood of normal individuals following the intravenous injection of typhoid vaccine and various other agents. On the other hand, Ludke and others have failed to demonstrate increased antibody formation in typhoid patients by non-specific agents. It has not been determined what particular element in the reaction is responsible for the increase in antibodies. The fever, leucocytosis, or the mere shock of the reaction have all been considered. Rolley and Meltzer (20) demonstrated that fever favored the formation of immune bodies. It is therefore possible that the rise in temperature might play a rôle. Ludke (21) observed that following recovery from an acute infection the antibodies disappeared from the blood but would reappear if the body temperature was increased. It is generally accepted that in order to secure striking results with protein therapy there must be a decided temperature reaction. In our experience the best results are observed after a decided rise in temperature. It is quite possible

that very moderate improvement may take place with very mild reaction. With specific vaccine administered subcutaneously the fever course in typhoid was often definitely modified. The results, to be referred to later, in certain acute infections with autohemotherapy where at most there is only a very slight temperature reaction, suggest that marked fever is not essential.

Reference has been made to the lack of relationship between the degree of leucocytosis and the benefit derived in pneumonia. At present it is impossible to determine whether a single factor or a combination is responsible for the results. For this reason the German term "shock therapy" is satisfactory. Weichardt (22), who has studied this subject for years, believes the reaction causes cellular stimulation with the mobilization of preformed specific and non-specific antibodies. The reaction brings about a combined activity of all protective agencies, a major effort to destroy the infection. Petersen has expressed this very clearly when he says, "no new defensive agents are formed but all defensive agencies are stimulated" (23).

Dollken (24) has modified Weichardt's theory by suggesting that different therapeutic results may be obtained with different non-specific agents. In other words, certain non-specific agents may be more efficient in a particular disease than other agents. Clinical experience fails to support this view. Typhoid vaccine may be used in all diseases where a foreign protein is indicated. The results obtained conform to those secured with a variety of other non-specific agents. The writer having tried a great variety of non-specific agents has returned to typhoid vaccine for all types of infection where non-specific therapy is indicated.

Weichardt's view of antibody mobilization presupposes the presence of antibodies in the patient. If antibodies are not available treatment will fail. The fact that not all patients are benefited should not discredit the treatment.

In addition to the general reaction following intravenous protein, there is a local reaction characterized by hyperemia, edema and pain in the infected area. This is illustrated in a case of acute polyarthritis where all but a few joints have returned to normal. Following the reaction the various healed joints may become temporarily red, swollen and tender. The involved joints are not infrequently tem-

porarily more painful Kolmer (25) suggests that this reaction is allergic in character, the healed joints having become sensitized

*Autohemotherapy* Before discussing the use of non-specific agents which produce a reaction, it might be well to consider some non-specific agents claimed to have therapeutic activity without producing a reaction

Blood after clotting behaves as a foreign protein to the host After separation of the serum from the clot the former may be injected intravenously or subcutaneously The whole blood citrated or uncitrated may be injected subcutaneously When the serum is given intravenously it not infrequently causes a reaction When serum or whole blood is given subcutaneously there is at most only a very slight rise in temperature, although it may excite considerable leucocytosis, at times preceded by a leucopenia, in other words, a miniature foreign protein reaction In addition to human serum, normal horse serum has been used as a non-specific agent Judging from the rather extensive literature, normal serum therapy has some value The results on the whole are less striking than are observed after protein shock therapy The absence of reaction permits its use in certain cases where a chill is undesirable The writer's experience with normal serum is limited to the effect of normal chicken serum in pneumonia This serum was kindly given to him by Dr H C Berger (26) The serum was administered intravenously in doses of 50 to 100 cc When there was no febrile reaction following the injection, there was no apparent benefit If the patient reacted with a chill, it might be followed by an immediate crisis

Kraus (27) and his colleagues have used normal beef serum in human anthrax An average of three injections were given at intervals of twelve hours, the average dose being 50 to 60 cc The serum was heated to 56°C in order to eliminate the "toxic effect" In 1921 he reported a series of 250 cases so treated with a mortality of 6.8 per cent as compared with 10 per cent when treated expectantly The lack of a striking difference in the mortality raises the question of the value of the treatment Furthermore, as bovine anthrax is quite prevalent in South America it is possible that beef serum contains specific immune bodies

Bingel (32), during the late war when it was difficult or impossible

to secure diphtheria antitoxin, used normal horse serum in alternate patients with diphtheria. Diphtheria antitoxin was administered to 471 patients, normal serum to 466. The mortality was the same in the two series. Calhoun (33) states that one cubic centimeter of normal horse serum has the same protective action as six units of diphtheria antitoxin. Three of these units can be accounted for by antitoxin normally present in horse serum and three units due to a non-specific reaction. Mackie (34) was able to protect guinea pigs against diphtheria toxin with a variety of normal sera, including guinea-pig serums.

Convalescent serum is employed in the treatment of scarlet fever. Moog (28), Rhode (30), and Schultz (29) have treated a limited series with intravenous normal human serum, claiming results closely approximating those obtained with convalescent serum. This method of treatment might be tried when convalescent serum is not available.

Rhode reports good results in pneumonia with autohemotherapy, injecting subcutaneously 50 to 60 cc of the patient's blood. In case there was no improvement within twelve hours he injected intravenously 1 to 2 cc of defibrinated blood. His report does not go into sufficient detail to create conviction. He treated 12 cases of erysipelas by this method without a failure. He reports a critical fall in temperature a few hours after the injection. Autohemotherapy has been used with reported success in typhoid, arthritis and acute encephalitis.

Autohemotherapy and auto serum therapy have been employed most extensively in dermatological conditions. Salutzki and Weiss (31) have recently reported their experience and those interested in this subject will find a complete bibliography attached to their paper. They obtained excellent results in acute eczema, unsatisfactory results in the chronic form. This treatment proved very satisfactory in acne vulgaris, sycosis simplex, and trichophytosis corporis. No benefit was noted in psoriasis, impetigo and lichen planus. This type of therapy on account of its simplicity and reported good results deserves further study.

*Roentgen therapy* Roentgen therapy has been employed in the treatment of acute infections, especially whooping cough. Its method of action is debatable. It may be considered a form of protein therapy, the protein arising from cells injured by the ray. Bowditch and Leonard (35) reported on 300 cases of whooping cough with 80

per cent benefited. The best results were obtained in early cases. Faber and Struble (36) in a very carefully controlled series were unable to observe any improvement.

*Agents employed* Mention has been made of the various agents used in non-specific therapy. One might gather from the literature that some of these are of special value in certain diseases. Milk is and has been largely employed by the ophthalmologists. This is readily explained by Muller and Thanner's early use of milk in parenchymatous keratitis. Other ophthalmologists followed this lead, probably not realizing that it was the reaction and not the agent employed that was important. A number of German proprietaries have been lauded as possessing special virtues in arthritis. The writer has not been able to verify their superiority. The results in all those that excite a reaction have been satisfactory, but none more so than typhoid vaccine.

All these agents may be considered non-toxic in the sense of serious injury to tissues. Mercurochrome, which was introduced as a specific in urinary tract infections, is now being used in practically all infections. Its action in the urinary tract is probably specific. Beyond this field its action is probably non-specific. In the blood it is changed to a form of mercury not highly germicidal, to be reconverted into mercurochrome when eliminated through the kidney into the acid urine. Todd (37) states that the acidity of the solution is highly important. With acidity near the neutral point it is almost inert. On account of its toxicity if its action is non-specific, its use should be limited to urinary tract infections.

*Dosage* The dosage of only two non-specific agents will be discussed, milk and typhoid vaccine. Milk was introduced by Schmidt and Saxl in 1916. Fresh or pasteurized milk is boiled or, some state, allowed to simmer for ten minutes and then cooled. It is never to be injected intravenously. The initial dose is from 2 to 5 cc, the dosage to be increased with subsequent injections. Rarely does the amount given in a single injection exceed 10 cc. The interval between treatments is from two to four days. The total course should rarely exceed five injections. If no benefit is derived after two or three injections, it is not probable that further treatment will be beneficial. If the improvement is progressive, the injections

may be continued until the patient is apparently cured or no further improvement is noted. Within five to six hours after the injection there is a chill, or at least a marked rise in temperature. The reaction resembles in every respect that observed after other foreign proteins. In certain individuals, as children or obese women, where intravenous medication is difficult milk may be used. The results are comparable with those obtained with intravenous protein therapy. There is one slight objection to milk, the danger of an anaphylactic reaction in a sensitized individual. The fear of sensitizing to milk as a result of treatment is not a valid objection.

The dosage of typhoid vaccine varies according to different observers from 25 to 250 million. The objective is a good reaction. When the writer began using typhoid vaccine the initial dose was usually 250 million. In recent years he has used as an initial dose 25 to 35 million. Rarely does such a dose fail to give a good reaction. A very violent reaction with nausea may follow a dose of 25 million. Each succeeding dose is increased by 10 to 15 million, as a slight immunity from a reaction standpoint develops. A good reaction is desirable, in fact, there is considerable evidence that a violent reaction will occasionally effect a cure when moderately severe reactions will give only temporary improvement. A patient with severe iritis was given repeated doses of 25 to 75 million with only temporary relief. By mistake the interne gave him 500 millions. The reaction was alarming but the iritis never returned. The author has had several similar experiences, where through error a massive dose was given which produced results that could not be brought about by moderate reactions. Such experiences are however exceptional. On many occasions when moderate reactions failed, massive doses were unsuccessful. The occasional value of massive doses should be borne in mind.

The above dosage applies only to afebrile or slightly febrile patients such as those with chronic arthritis. If we are treating an acute infection with high temperature, as pneumonia, typhoid or erysipelas, the initial dose should be smaller, not to exceed 15 or 20 million. Even these small doses may cause a rise in temperature of two or three degrees Fahrenheit. Perhaps this precaution in regard to dosage is

unwarranted and may at times fail to give results where a larger dose would be effectual. It has the advantage of being safe.

The importance of a good reaction is emphasized and it is essential if we wish to get dramatic results. It should not be overlooked, however, that smaller doses given daily may more gradually effect a cure with less inconvenience to the patient. Holler's treatment of typhoid fever with small daily doses will be referred to later.

The interval between treatments varies from two to four days. This interval is quite arbitrary, theoretically merely a sufficient interval to give an opportunity for formation of new antibodies. The longer the period the greater the number of antibodies to be mobilized. The four day interval permits the patient to regain his strength and prepare him for the next reaction.

*Dangers* Is foreign protein therapy dangerous? The author has administered or supervised the administration of foreign proteins during the past ten years to several hundred patients without a fatality directly due to the treatment. One patient, an alcoholic with arthritis, following the reaction developed delirium tremens and then pneumonia and died. This is the only fatality traceable indirectly to the reaction. Chronic alcoholism may be considered a contraindication. The writer has never observed an anaphylactic reaction following typhoid vaccine, although not infrequently there may be an interval of ten days or more between injections. Elderly people with evidence of an impaired myocardium have not been treated. The same holds true of patients who have suffered for a long time from an exhausting infection. A compensated valvular lesion is not considered a contraindication. In very acute infections, as pneumonia, we should begin with a small dose in order to determine how the individual will react. The writer has seen some very severe reactions,  $108^{\circ}\text{F}$ , in a typhoid without serious consequences except alarm on the part of the physician. As this patient had an immediate crisis without return of fever the results may have partially warranted the unintentional heroic treatment. Such severe reactions can and should be avoided in spite of the belief that severe reactions are very likely to be beneficial. With proper dosage and selection of patients the foreign protein is not a dangerous therapeutic agent. Failure to observe these precautions may lead to serious consequences.



## CLINICAL RESULTS

*Acute and chronic arthritis.* Non-specific therapy has been used more extensively in arthritis than in any other disease. In acute arthritis the results are often dramatic. A helpless patient may within two or three hours following the reaction be quite comfortable. About 70 per cent of patients with acute arthritis are practically free from discomfort or at least greatly relieved after two or three injections of typhoid vaccine. In about 35 per cent of these relief is permanent. In the others following an interval of a few days to several weeks the arthritis recurs. These late recurrences are probably reinfections. The early relapses may be interpreted as due to incomplete destruction of the infecting agent. The writer has endeavored to eliminate these relapses by giving several treatments after the patient has apparently recovered but without success. Experience suggests that it is difficult or impossible completely to immunize this group. The results in acute gonorrheal arthritis in the experience of the author are not as satisfactory as those obtained in ordinary acute arthritis.

The method of treatment employed by the writer is to give an initial intravenous injection of 25 to 35 million. If there is a good reaction the patient is given a second treatment of 35 to 45 million in two to four days. This increase in dosage is essential in order to secure a good reaction. In case the patient shows definite improvement, the treatment is continued with increasing doses until he is entirely relieved or the progressive improvement comes to a standstill. In case of relapse treatment is instituted with the first evidence of return of symptoms.

In case no improvement is noted in the initial treatment following two good reactions, the treatment is discontinued because only rarely will further treatment be beneficial. In some of those apparent failures a few days following the discontinuance of treatment marked improvement may develop and under these circumstances the patient is given two or three additional injections.

Protein therapy is of value in acute arthritis and is apparently the only means of aborting this disease as it is highly probable that salicylates relieve symptoms but do not shorten the course of the disease. When care is exercised to avoid treating cases with marked acute endocarditis there need be no menace to the patient.

There is a very extensive literature on the non-specific treatment of acute arthritis and the authors are in agreement in regard to the value of this method in selected cases (Miller and Lusk (38), Cowie and Calhoun (39), Gore (40), Culver (41), and many others) In addition to typhoid vaccine numerous other agents have been used, as milk, sodium nucleinate, albumose, colloidal metals, and numerous proprietary preparations A study of the literature does not show that any of these agents are superior to typhoid vaccine

*Chronic arthritis* On the whole the results of non-specific therapy in chronic arthritis do not excite great enthusiasm If patients are carefully selected, worthwhile results may be obtained in a limited number of cases The more recent the onset and the greater the evidence of activity in the joints the better the prospects It is needless to state the treatment is futile in chronic osteo-arthritis, without evidence of active infection in the joints Chronic arthritis of less than a year's duration, without exostoses and especially where only a few joints are involved, may be decidedly benefited by non-specific therapy In a considerable number of such cases the infection can be eliminated and with the aid of heat and massage the joints may be restored to their former usefulness Some of these cases may relapse but as a rule renewed treatment will give good results Several patients of this type, apparently progressing toward a high degree of disability, have been free from arthritis for several years Gonorrheal monarticular arthritis of months' standing with very marked stiffening of the involved joint may yield in a remarkable manner to the treatment I have seen a wrist almost rigid and edematous for months clear up completely after two or three reactions Needless to say in these cases only the periarticular structures are involved In patients where the disease is of several years' standing and where some of the joints present evidence of acute or subacute inflammation, protein therapy may relieve this active process As a rule, however, within a few weeks the old inflammatory condition recurs The results in this type of case are unsatisfactory The above discussion is based on the writer's personal experience Some physicians are much more optimistic regarding the value of non-specific therapy in chronic arthritis

Yoeman (42) recently reported a series of 50 cases of subacute and

chronic arthritis with improvement in from 80 to 90 per cent. In 50 to 60 per cent of these the improvement was maintained. He states that the subacute types where the disease is confined to the periarticular structures are the most hopeful. Perhaps his results were achieved by a very careful selection of patients.

Stockman and Campbell (43) report a series of seventy-three cases, both acute and chronic, with 40 cases permanently benefited (one to three and one-half years). They obtained the best results in those cases of chronic arthritis where the disease began in an acute form. When the onset was insidious if any improvement was noted it was usually only temporary.

Fliegel and Strauss (44) report a series of patients with chronic arthritis treated with Mirion (a preparation containing gelatin and iodine). They claim "cures" in 50 per cent of this group. Biencke, using this same preparation, reports 25 per cent of cures. He states there is no relationship between the presence or absence of a reaction and improvement in the patient. The writer has used Mirion and has only noted improvement when a reaction took place. The most probable explanation of the high percentage of cures is the careful selection of cases for treatment. It is highly improbable that it was due to the particular non-specific agent employed.

*Pneumonia* The value of non-specific therapy is of special interest as it raises the question whether the favorable action of so-called specific sera and antibody solutions is due to their specificity. Leaving out of the question the possibility of benefit without reaction, it has not been determined satisfactorily whether patients who have a febrile reaction after serums are more apt to be benefited than those who do not react. That the course of pneumonia may be modified following a protein reaction is well established. Ludke (46) noted an immediate improvement in five out of ten pneumonias following the intravenous injection of 1 to 3 cc. of a 10 per cent proteose. Von den Velder (47) and Pitz and Munzer (48) have reported definite results in bronchopneumonia following the intramuscular injections of milk. Freeman and Hoppe (49) report striking results in pneumonia of children with mercurochrome and Gardner-Medwin (50) has precipitated a crisis in pneumonia with subcutaneous injection of sodium nucleinate. This list does not by any means exhaust the literature on this subject,

many writers furnishing evidence of therapeutic action. The writer treated fifteen consecutive cases of lobar pneumonia within forty-eight hours or less of the onset with a single intravenous injection of typhoid vaccine. All reacted with a rise in temperature and leucocytosis. In six patients the pulse, temperature and respiration returned to normal a few hours after the reaction. The patients appeared detoxicated. The improvement was temporary in three of these, as within twelve to twenty-four hours the symptoms returned with unmodified severity. Three patients were permanently detoxicated and underwent rapid convalescence. They continued to run about one degree of fever and the lung remained consolidated until the time when the crisis normally would have developed. This peculiar phenomenon of detoxication with delayed resolution is present as far as I have been able to determine in all patients who show improvement following the use of so-called specific sera.

The various specific sera are usually given intravenously and a reaction is not unusual. Kyes' (51) immunized chicken serum lowered the mortality in pneumonia, and the series on the whole was well controlled. A chill or a marked reaction frequently followed the treatment. The serum was later modified by removing the fibrin, which in a large measure eliminates the reaction. It will be interesting to determine whether the value of the serum has been lessened by this change.

Larson (52) has prepared for experimental purposes an immunized sheep serum. It is given intravenously in doses of 50 to 100 cc. He reports that frequently but not always there is a definite reaction. He reported a number of crises after a single injection. Through the courtesy of Dr. Larson the writer was supplied with the serum. Twelve early lobar pneumonias were given 50 to 100 cc intravenously. In some patients this dose was repeated. None of the patients had a reaction and as far as could be determined the course of the disease was not modified.

Huntoon's antibody solution has been used in the treatment of pneumonia by Cecil (53) and Connor (54). This solution is supposed to contain antibodies for pneumococcus types I, II and III but not for type IV. Following its intravenous injection there is a severe reaction, the temperature in one case reaching 109°F. Following the

reaction the patient perspires freely, the temperature falls to normal or subnormal and in some cases the disease is immediately terminated. They were able to lower the mortality as compared with controls. On account of the danger associated with the reaction they concluded that this was not a safe method of treatment. They had a few fatalities which they thought were directly due to the reaction.

Cecil and Baldwin (55) having decided that the intravenous injection was too dangerous tried the subcutaneous method. They reported that the bacteremia was favorably affected, but this improvement was noted also in type IV, although antibodies for this type were not present in the antibody solution. The mortality of all types of pneumonia was reduced as compared with the controls during 1923 when treatment was begun within forty-eight hours of the onset. Here again striking results were obtained in type IV, much better than in types II and III, but not as good as type I. In the 1924 series, forty-eight hour cases, if type IV is excluded the mortality in the treated cases was 41.1 per cent, in the untreated 43.7 per cent. Summing all cases, both early and late, treated during 1923 and 1924, the mortality in the treated cases was 34 per cent and in the control 35 per cent. The authors state, "in this table only type IV pneumococcus pneumonia shows a death rate favorable to antibody treatment." We have here again an agent that is apparently only beneficial when followed by a reaction—no reaction, no results.

Dorothy Rhoades (56) in the Hygienic Laboratory was unable to demonstrate protective substance to type I pneumococcus after the subcutaneous injection of 400 cc of antibody solution.

*Typhoid fever.* Attention has already been called to typhoid as the disease where the effectiveness of non-specific therapy was first demonstrated. Since then there has developed an extensive literature, clearly demonstrating that the course of the disease can be modified even to immediate termination. It is also maintained that the mortality is lowered. Approximately 20 per cent of cases terminate by crisis following a single reaction, 20 per cent more by rapid lysis, in another 20 per cent the fever becomes irregular, the severity of the disease lessened and its course shortened. The remaining 40 per cent are not modified. Accepting the present theory of action, these either do not have available antibodies or the reaction fails to mobilize them.

As in pneumonia the treatment is attended with some risk. The writer has treated typhoid by this method and observed the sudden termination of the disease and has never seen any ill effects. A temperature reaction to 108°F gives rise to uneasiness and the responsibility is too great. Those who have the courage to try it should begin with a very moderate dose, not more than 15 million typhoid bacilli. A safer method of treatment is to give large doses intramuscularly, enough to excite a good local reaction and a moderate general reaction. Holler (57) has used very small doses intravenously, just enough to excite a mild reaction. In the beginning he gives two treatments daily and after a few days one treatment daily, continuing it until the fever is broken. In 1917 he reported 350 cases treated by this method with a mortality of 0.5 per cent and an average duration of the disease of only ten days. All of his patients came under observation early and this accounts in part for his good results. He employed a ten per cent solution of deutro-albumose, beginning with 1 cc and gradually increasing the dose, carefully avoiding a marked reaction.

*Sepsis* It would scarcely be thought that a condition like sepsis, frequently accompanied by chill, would be benefited by protein therapy. The temperature reactions of the patient with sepsis are apparently the counterpart of those following protein therapy. Nevertheless, there are many advocates of the value of protein therapy in this condition. There is no reason to doubt the accuracy of their observation. Reference will therefore be made to a few of the many reports in the literature. Ludke treated five cases with three rapid recoveries. Wilmette (58) reports a series of cases of puerperal sepsis with good results, several terminating by crisis. Jacob and Wendt (59) treated seven patients with severe sepsis by the subcutaneous injection of turpentine, causing a localized abscess. They are quite enthusiastic about this treatment and believe it is frequently a life saving procedure. Mercurochrome has been used very extensively in septicemia, and with reported good results (Polak (60)).

*Erysipelas* Petersen, Jobling and Manier treated erysipelas with proteins in 1915, and later Petersen reported a series of 15 cases treated with proteins, milk or typhoid vaccine, with striking results in some cases. Holler, following the method he used in typhoid, treated 32 cases with small daily doses of albumose with gratifying results.

Blumenau (61) treated a series of 77 cases with sodium nucleinate with improvement in the patients' general condition without much change in the local process. Petersen refers to a series of 52 cases treated by Schmidt with milk injection. In 27 of these defevescence began within twenty-four hours of the first injection and 12 more within three days. The earlier the treatment is instituted the better the results.

*Gonorrhea and its complications* have received considerable attention from those interested in non-specific therapy. It has long been recognized that an acute intercurrent infection may favorably influence the course of a gonorrhea. Here as in other acute infections a variety of non-specific agents have been used. In epididymitis very excellent results have been reported. Less striking improvement has been observed in tubal infections.

*Bacillary dysentery*. This very stubborn disease is reported to yield to non-specific therapy. It is generally conceded that treatment with specific serum is far from satisfactory. During the late war dysentery was treated very extensively by non-specific agents. Nolf (62), who found specific vaccine given subcutaneously of little value, resorted to intravenous administration. This gave the characteristic non-specific reaction and very good results. Ludke treated 15 cases (13 Shiga, 7 Flexner) with albumose, with 5 rapid recoveries. Many other references might be given, all testifying to the value of non-specific therapy. In this disease where previous methods of treatment are not satisfactory protein therapy should be seriously considered.

*Peptic ulcer*. At first thought it would appear highly improbable that protein therapy could be of value in gastric or duodenal ulcer. If we accept the view that peptic ulcer is of bacterial origin this treatment is not illogical. A study of the literature brings the belief that ulcer symptoms may not only be promptly relieved but in some cases the ulcer actually cured by this treatment. Whether this should be accepted as evidence that peptic ulcer is of bacterial origin does not necessarily follow. Pribram (63) explains its action on lessening of the irritability of the sympathetic, thus lessening vascular spasm. The evidence on this point is not convincing. He used a vegetable protein in dosage sufficient to excite only a mild reaction. Any other protein

## NON-SPECIFIC THERAPY

would probably answer the purpose. The patients were kept on a general diet without alkalis. He reported 300 cases and states that with few exceptions the pain was at least temporarily relieved after a few injections. Ulcers of the lesser curvature gave the best results. Next, pyloric ulcer, duodenal ulcers were the least satisfactory. He states that good results were observed in 50 to 60 per cent. A considerable number of these relapsed but by repeating the treatment permanent benefit was finally obtained. Roentgen ray observations indicated that the ulcer was healed. The treatment was given at two to four day intervals, the patient receiving a total of eight to ten injections. After the lapse of four weeks the patient was given another course of six treatments. Holler (64), Perutz (65) confirmed Pribram's observation. Recurrent hemorrhage is a contraindication, but he reports that hemorrhage has never been observed as a consequence of the treatment.

The writer has tried this treatment in a desultory manner on several stubborn duodenal ulcers. The patient was placed on the ward and without alkalis. Typhoid vaccine was given intravenously in doses of 25 million. Several of these patients were entirely relieved of their discomfort after one or two injections and could be kept comfortable as long as the treatment was continued. It was impossible to follow them up after leaving the hospital but some of them at last relapsed and reentered the hospital. The prompt relief from all discomfort was striking. It might be claimed that the relief was due to lowering gastric acidity. Jacoby (66) was unable to detect any change in the normal on the secretion of hydrochloric acid or pepsin following intravenous protein therapy.

*Encephalitis* Good results have been reported by Dannhauser in acute encephalitis. Leiner's (68) results with postencephalitic mental changes is most interesting. His attention was attracted to this treatment after observing a recovery following pneumonia. In his report he has used protein therapy in 23 patients of this type and reports very gratifying results.

*Ophthalmology* Non-specific therapy, especially in the form of milk injections has been used extensively in iritis, keratitis, choroiditis and conjunctivitis. Müller and Thanner (69) reported good results in all these conditions, and especially satisfactory in acute iritis.



Jacovides (70) treated 150 corneal ulcers, 140 of which were cured after two or three injections. Huber observed that patients with trachoma were greatly benefited after recovery from scarlet fever. He then treated a series of patients with milk and reported good results. Friedlander (71) reports a series of 42 cases of trachoma with very satisfactory results. Specific ophthalmia yields to non-specific therapy. In the writer's experience there is no acute infection in which the results are so uniformly good as in acute iritis. The improvement is usually immediate and the relief permanent.

*Dermatology* Reference has been made to autohemotherapy in dermatitis. In addition, shock protein therapy has been employed with reputed benefit in ringworm, pruritus and lupus. Fischl (72) reports good results in ringworm with subcutaneous injections of 0.2 cc of 20 per cent turpentine. The resulting local abscess acts as a foreign protein. Pruritus ani has been treated by Murray with subcutaneous injections of *streptococcus faecalis* vaccine. He refers to this as specific vaccine therapy. The writer has noted good results with intravenous typhoid vaccine, but has considered it as a non-specific desensitization. Kolmer (73) has used intramuscular injections of 5 to 10 cc of sterilized milk successfully.

*General paresis* Wagner-Jauregg's treatment of paresis has created a new interest in non-specific therapy. Paresis has been considered an incurable disease. When the syphilitic origin was recognized it was hoped that antisiphilitic treatment with mercury and iodides might be beneficial but it soon was apparent that such therapy was of little if any value. With the introduction of arsenicals hopes were again raised, but soon to be followed by disappointment. The mental symptoms requiring institutional care make this disease unusually distressing to friends and physician.

Long before the etiology of paresis was understood it has been observed that following a severe infection the paretic often showed marked improvement and in a few instances permanent cure. Halban (74), in 1802, collected a series of "cured" paretics, the majority of whom had previously had some severe acute infection or prolonged suppurative process.

Hippocrates relates that patients with mental disorders were often greatly improved following an acute fever. If we accept the view

that syphilis was introduced into Europe by the sailors of Columbus, none of these patients had paresis Gerstmann (75) states that both Boerhaave and Sydenham noted the beneficial effects of fever in psychoses Kostel, in 1856, reported improvement in psychoses following smallpox and Schlager, in 1857, after typhoid fever He states that 6 of 11 patients in an institution who had typhoid were cured

Schroeder Van Der Kolk, in 1863, reported the recovery of a patient insane for five years following measles Nasse, in 1870, reported 10 out of 21 mental patients cured following typhoid and 5 temporarily benefited Rosenblum, in 1874, reported 4 psychoses greatly benefited after intermittent fever and 1 following typhus fever He also reports recovery in a number of chronic psychoses following inoculation with recurrent fever Schule, in 1875, refers to a patient with paralysis cured and able to return to work following gangrene of the lung At the time the report was made the patient had been under observation for five years Flemming, in 1877, reported a seven year remission in a paretic following typhoid Gerstmann discusses many other instances of recovery in mental disorders following acute infections It is not known whether all these had paresis

Wagner-Jauregg became interested in the relation between infections and improvement in paresis and in 1887 published an article on "The action of febrile diseases on psychoses" (76) This included not only a review of the literature but also some personal observations Since this time he has persistently studied this subject, using various means for exciting febrile reaction His faith in the possibilities of this form of treatment is admirable He first attempted to inoculate paretics with erysipelas, but was unable to produce more than a slight reddening of the skin A year later he tried Koch's tuberculin Ten years later he made a report on 69 patients treated by this method He thought he was able to produce more frequent and prolonged remissions but no cures In his earlier cases he avoided marked reaction Later he attempted to secure a more marked reaction He was unable however in many patients to obtain repeated good reactions With this modification of the treatment he obtained some "lasting" remissions and the patients were able to leave the institution and return to work

Meanwhile Pilcz, in 1911, reported a series of 86 patients treated with tuberculin with 26.7 per cent greatly improved and 23 per cent where the disease came to a standstill. The improvement however was rarely permanent.

Later Wagner-Jauregg used Besredka's polyvalent typhoid vaccine. This vaccine contained living typhoid bacilli, their virulence reduced by mixing with typhoid immune serum. This was given intravenously beginning with 25 million and gradually increasing to 500 million. He was able to obtain good febrile reactions. The injections were given every second day until the patient had received eight to twelve reactions. The frequency, degree and duration of the remission were much better than with tuberculin.

Meanwhile Donath and Fisher independently treated a series of paretics with intravenous sodium nucleinate. They were able to secure marked reaction and leucocytosis. The remissions were prolonged but apparently not permanent.

Wagner-Jauregg inoculated his first patient with malaria in 1917. In 1919 he reported on 9 cases. Four of these were greatly improved and 2 of them in 1925 were still working at their former occupations. In 1 of these the pupillary reflex became normal. The other 2 improved patients later relapsed, 1 died, the other came to a standstill. Since 1917 he has used malarial inoculation almost exclusively in the treatment of paresis as his results were better than in any of the previous methods. He states that with typhoid many patients became immune to the treatment and he was unable to obtain good reaction.

Kunde and Gerty (77) have recently been able to obtain good reactions in paretics by injecting increasing doses of typhoid vaccine beginning with 50 million and increasing to one and one-half billion. If the results should prove as satisfactory as with malaria, it would greatly facilitate the more general use of protein therapy in this disease. It has a number of advantages, the frequency of the chills can be regulated, the patient does not develop a marked anaemia and we are not dealing with a living parasite which must later be destroyed. The mortality from the malarial treatment is 8 to 12 per cent, and in some patients the treatment must be interrupted or discontinued. With typhoid vaccine there should not be any mortality, especially if the

interval between chills is properly regulated, allowing the patient to recuperate between reactions

By 1925 Wagner-Jauregg had treated 1000 patients. His results are especially interesting as practically every parietic was treated and not merely selected cases. His results have recently been presented in monograph form by Joseph Gerstmann. In this report he includes the 400 cases treated previous to 1924, thus all the patients had been under observation from two to six years since the treatment was discontinued. Following or associated with the malarial treatment each patient received six injections of neoarsphenamin, or a total of 3 grams.

One hundred thirty-two patients, or 31 per cent, had complete remissions and have returned to their previous occupation and are able to carry on in a normal manner. Fifty-seven, or 14.2 per cent, had incomplete remission, were able to return to work but not to their previous occupations. They were able to earn a livelihood but mentally were somewhat below normal. Apparently all these patients have been carefully followed and these figures may be accepted as indicating what can be accomplished in unselected cases of general paresis. A much longer period of observation is required before it can be stated that the "cure" is permanent. Even if many or all of these should relapse the treatment is still worth while. Wagner-Jauregg believes that the percentage of cures would have been much greater if he had confined his treatment to selected cases. In those having a complete remission the duration of the disease ranged from a few months to three years. In those not benefited the duration of the disease was one to six years. Some patients who recovered had been in the institution three years.

The next largest series of cases which has been carefully followed for a considerable time is that of Weygandt (78) and Muhlens (78) of the psychiatric clinic in Hamburg. They began the malarial treatment in 1919. They report 31.1 per cent able to return to their previous occupations and 21.4 per cent greatly improved. Nonnes von Reese and Peter (79), in 1924, reported on 75 patients selected from a group of 236 parietics. They report good remissions of one and one-half to two years' duration in 70.5 per cent. They treated only selected cases. In going over ten reports from American and English sources there

was a striking similarity in the reported "cures," approximately 30 per cent.

It is perhaps unnecessary to state that the malarial treatment is probably a form of foreign protein therapy. The protein is derived from the destroyed corpuscles and the body of the parasite.

Hoff and Silberstein (80) following a malarial chill in a paretic found increased bactericidal activity of the blood serum for staphylococcus, streptococcus and colon bacillus. The spinal fluid plus leucocytes from the patient destroyed the *Spirocheta pallida* in a few minutes. A piece of luetic testicle from a rabbit placed in such a mixture loses its power to infect a normal rabbit. No spirocheticidal substance could be detected in the non-syphilitic following a malarial chill.

Curiously, there is little if any relationship between the clinical changes in the patient and the spinal fluid findings. A marked improvement in the spinal fluid has little prognostic value and is often temporary. A patient of Wagner-Jauregg who has been mentally normal since 1918 shows very little improvement in the spinal fluid. As a rule in those cases where the remission is prolonged, the cells in the spinal fluid drop and the globulin reaction is lessened, thus showing lessening activity of the infection, but the Langegold curve and the Wassermann reaction may be little modified. Occasionally the spinal fluid gradually returns to normal. These findings correspond very closely to those observed in paresis after treatment with tryparsamid. Gerstmann reports that the brain tissue of patients with a remission dying from an intercurrent disease shows a tendency to return to normal; in other words, the clinical and anatomical improvement is in accord.

Gerstmann comments on the great frequency of syphilis in tropical and subtropical climates and the great infrequency of central nervous system involvement. He suggests that this may be due to the prevalence of a variety of acute infections. In Java where syphilis and malaria are both prevalent paresis and tabes among the natives are practically unknown. In certain districts in China were practically all the inhabitants have or have had malaria, Bercourtz states that he has never seen a patient with paresis and only a very few with tabes. Plaut and Steiner (81) were first to try inoculation with African

relapsing fever in the treatment of paresis. This disease is self-limited, subsiding after three to four fever recurrences. The elevation of temperature, which may reach  $104^{\circ}$  to  $105^{\circ}\text{F}$ , persists for two to four days. The reaction is not so severe as in malaria and is better tolerated by the patient. One objection offered is that the patient acquires a prolonged immunity and the treatment cannot be repeated as is possible in malaria. They reported a series of 76 cases treated previous to 1924. Thirty-four, or 45.8 per cent, were so much improved that they were able to leave the institution. Twenty-six of these, or 34.2 per cent, had complete remissions. It is not stated whether this series included only selected cases.

Solomon, Beck, Theiler and Clay (82) recently reported on the use of *Spirochaetæ morsus-muris* (the microorganism of rat-bite fever) in paresis. They considered malaria not satisfactory on account of the difficulty of having the parasite always available, the severity of the reaction and the secondary anemia. Relapsing fever was not satisfactory as they were unable to secure cultures sufficiently virulent to give a good febrile reaction. Apparently one reason for selecting the microorganism of rat-bite fever was that they were using a spirochete. This is not well-founded, as it is apparently the reaction and not the agent exciting it that is important.

This spirochete is easily kept alive in the ordinary laboratory animals, gives a good febrile reaction, is not especially dangerous in man, and can be readily destroyed with arsphenamin. They report a series of 12 paretics, but the remissions have not been of sufficiently long standing to draw any conclusions in regard to their permanency.

The results obtained in paresis have led to clinical observations with non-specific therapy in other psychoses. If our present conception of the mode of action is correct we would not anticipate benefit except in those psychoses associated with an infection. In the rather extensive literature on the effect of acute infection in mental disorders, the particular type of psychosis is usually not mentioned. This is especially true in the older literature.

*Dementia praecox*. There is a limited literature on non-specific therapy in dementia praecox. There is still some discussion as to whether there is spontaneous recovery in this disease. Schmid (83), who apparently had unusual opportunities to follow cases as he

was stationed in an asylum taking care of all mental cases for a canton in Switzerland where patients who relapsed were returned to the institution, reports 16.2 per cent of 455 patients with dementia praecox as recovered. This is important in evaluation of the cures reported by special methods of treatment.

Rosenfeld (84) recently reported on the effect of an epidemic of typhoid fever in the psychiatric clinic at Rostock. He states that a number of psychiatric patients including dementia praecox showed marked improvement, in fact in a few cases complete recovery. In at least two cases the improvement was still present after the lapse of two years.

Templeton (85) has briefly reviewed the literature and reported his own experience. He refers to three series of cases treated with sodium nucleinate, one by Lundvall of 13 patients with 4 recoveries and 9 improved, another by Donath of 14 cases with 3 recoveries and 9 improved, and the third by Levin of 13 cases without any benefit. Templeton treated 20 cases with malaria. A number of patients showed remarkable improvement, in some cases a return to normal, but within two to five months all relapsed. It would be interesting to know whether further treatment might have given more prolonged recoveries.

*Early syphilis.* Berde (86) studied the effect of malaria on early syphilis. The primary lesion disappeared more rapidly than under ordinary treatment and the spirochetes disappeared from the tissues. In 9 out of 10 cases of secondary syphilis the lesions rapidly disappeared but the improvement was only temporary. Greenbaum and Wright (87) using milk were able to make the secondary lesions disappear in some patients but in others they were stimulated. Gummatous lesions disappeared rapidly.

Apparently non-specific therapy has a decided action in early spinal cord lues. In Finger's clinic when the spinal fluid was positive in early syphilis, they found malaria the most efficient method of rendering it negative. Kyrle recommends combined specific and non-specific therapy in resistant syphilis, especially of the central nervous system.

*Tabes dorsalis.* Wagner-Jauregg (88) is not enthusiastic over the malarial treatment in tabes, although he reports disappearance of the

lightning pains and crises He sums up his experience with non-specific therapy as follows

The most valuable form of non-specific therapy in paresis is malarial inoculation, next African recurrent fever In the treatment of severe types of paresis malaria and recurrent fever are so superior to other methods that they are now being used exclusively in his clinic This method of treatment is also used as a prophylactic measure in patients with positive spinal fluid but without signs or symptoms of tabes or paresis This treatment may be used in selected cases of tabes It is still to be determined whether the treatment is of value in true brain and spinal cord syphilis

*Multiple sclerosis* The etiology of multiple sclerosis has not been determined There is, however, an increasing tendency to look upon it as infectious in character If so, non-specific therapy might be beneficial Gross (89), a student of Wagner-Jauregg, treated one series of cases with typhoid vaccine and other series with malaria The typhoid series included 29 patients of the chronic progressive type, none of whom had ever shown any tendency to remission Twenty-seven per cent of these showed very marked improvement The more recent the onset the better the results

Forty-two patients were treated with malaria followed by a course of six injections of neoarsphenamin In the acute type marked improvement was noted in 26 per cent and moderate improvement in 46 per cent In the chronic progressive type 16.6 per cent definitely improved, 4.1 per cent slightly improved After the treatment was discontinued the improvement was progressive and up to the time the report was made there were no relapses

Schacherl (90) treated 64 cases with combined typhoid vaccine and neoarsphenamin and reported 62.5 per cent definitely improved, 25 per cent moderately improved

Dreyfus and Hanan (91) treated two series, one with typhoid and one with malaria, in each instance followed by one course of neo-salvarsan In the typhoid series of 10 cases each patient received twenty intravenous injections of typhoid vaccine Seven of these patients were of the chronic progressive type and had received previous treatment with neoarsphenamin without benefit Two of this





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Forty-two patients were treated with malaria followed by a course of six injections of neoarsphenamin. In the acute type marked improvement was noted in 26 per cent and moderate improvement in 46 per cent. In the chronic progressive type 16.6 per cent definitely improved, 41 per cent slightly improved. After the treatment was discontinued the improvement was progressive and up to the time the report was made there were no relapses.

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type were definitely improved, with no tendency to relapse after a period of seven months. One progressive case came to a standstill and four were not benefited. Three patients with a history of remissions were all very much improved. One of these was able to return to her previous occupation of pattern maker. Another patient had been entirely relieved subjectively and objectively for one year. The third patient relapsed.

Twelve patients were treated with malaria. Ten of these were chronic progressive in type and 2 were of the relapsing form. The progressive cases had previously been given neo-arsphenamin and some of them typhoid vaccine without benefit. Each patient was given from nine to twenty chills and during this time received 3 grams of neoarsphenamin. Two patients were greatly benefited and 9 definitely improved, 1 of these later relapsing, but the other 8 still maintained their improvement after the lapse of three to six months. All of these patients had been under observation from one to five years and never had a remission. The result in the 2 of the relapsing type was not definite.

This is a new field in which non-specific therapy offers some hope. If the disease can be brought to a standstill it will mean much. If the treatment is begun early before irreparable tissue changes have taken place, complete recovery may be possible. In long-standing cases with tissue damage, stopping the progress of the disease is all that can be expected.

#### NON-SPECIFIC DESENSITIZATION

There is increasing evidence that desensitization is not strictly specific. Whether the desensitization is as complete or as enduring when a non-specific agent is employed is open to discussion. That it occurs, however, can scarcely be denied.

Biedl and Kraus (92), in 1909, found that animals sensitized to a foreign serum could at least be partially desensitized with peptone.

Weil (93) demonstrated that a preliminary injection of sheep serum may protect guinea pigs against the sensitizing action of immune rabbit's serum.

Pfeiffer and Mita (94) were able to desensitize with swine serum an animal previously sensitized to horse serum.

Lewis (95) observed that an amount of protein necessary to cause anaphylactic shock would not act if injected with or twenty-four hours following the injection of some other protein

Karsner and Ecker (96) were able to show that whereas a certain degree of desensitization could be obtained with a heterologous serum, it was not as complete or lasting as with a homologous serum

Dale (97) demonstrated that the uterus of a guinea pig previously sensitized to several sera and in addition to egg-white could be desensitized to the sera with egg-white

Non-specific desensitization may be of great aid to the physician in treating recognized sensitization diseases, as asthma, where the sensitizing agent cannot be determined. It may also be helpful in diseases of unknown etiology where the possibility of their anaphylactic nature is suspected, as migraine (98), epilepsy (99), and intermittent hydrarthrosis (100), by enabling the physician to test out his theory with non-specific agents

*Asthma* Non-specific desensitization in asthma has been rather widely discussed, especially in those cases where the nature of the sensitizing agent cannot readily be determined. Various non-specific agents have been employed as stock vaccines, peptones, normal horse serum, autoserum, milk, snake venom, tuberculin, etc. There can be little doubt that desensitization can be carried out by any of the above agents but not by any means in every case, since specific desensitization very frequently fails. Specific desensitization in hay fever has not been the boon formerly anticipated. Not infrequently following a prolonged fever, as typhoid, an asthmatic may be free from seizures for months. Recently the writer saw a patient with asthma who had tried out specific desensitization without benefit. He had daily seizures for more than a year. He acquired a pneumonia complicated by empyema, his asthma completely disappeared to return shortly after the empyema healed.

Asthma may be greatly relieved during pregnancy. This may be due to non-specific desensitization from the placenta which it is known behaves toward the mother as a foreign protein.

A patient on my service at Cook County Hospital had continuous asthma for more than a year, requiring three or four hypodermics of suprarenalin daily. Both specific and non-specific desensitization

failed to relieve him. He acquired diphtheria and following the injection of antitoxin was entirely relieved of his asthma for about two weeks when it returned.

Kahn and Einsheimer (101) reported good results in asthma with autohemotherapy. They injected 20 to 30 cc of the patient's blood subcutaneously. The blood after coagulation behaves as a foreign protein. The literature contains several references on the favorable results in asthma with this treatment. The patient receives a total of ten injections at four-day intervals. In case the patient is relieved he may continue to receive injections at two weeks' interval, or stop treatment until the asthma returns, when two or three injections will be sufficient to control the discomfort.

There has been considerable discussion on autogenous as compared with stock vaccines. It is the writer's experience that a patient who is not benefited by stock vaccines will not be relieved with autogenous vaccine.

Rackeman (102) believes vaccine in asthma is beneficial in proportion to its powers to produce a local reaction at the site of injection. He has failed to get results except when the dosage is sufficiently large to produce a local reaction. He considers the reaction and not the agent exciting it as the essential factor. Such a subcutaneous reaction might in itself give rise to a foreign protein which could be a factor in the desensitization.

Van Leeuwen (103) is a strong advocate of tuberculin in the treatment of asthma. In case the patient has a negative von Pirquet test the initial dose is 1 cc of 1-100,000 solution. He repeats the injection twice a week, increasing each dose by 0.1 cc, always avoiding a general reaction. In his recent book on allergic disease he reports 300 unselected cases of asthma treated by this method with 50 per cent completely or almost completely cured and 25 to 30 per cent more distinctly or considerably improved. It is difficult to explain the "permanent cures" reported by various writers. As now understood desensitization is a temporary state.

Auld (104) reported good results in asthma with intramuscular or intravenous injection of Armour's peptone. Witte's peptone is not suitable on account of its greater proteose content. This may be given

intramuscularly, beginning with two minims and gradually increasing to twenty minims

Schiff (105) has reported good results in asthma by the intramuscular injection of milk

Spangler (106) advocates rattlesnake venom (Crotalin) in asthma. The venom contains peptone and a globulin and may therefore be considered as a form of non-specific desensitization

The writer has never been able with either specific or non-specific desensitization to observe striking results in asthma. The course of the untreated case should be considered. The most frequent type of bronchial asthma in adults accompanies a bronchitis, when this subsides the asthma is relieved. Any method of treatment extending over twelve weeks might be given unmerited credit. In the real chronic asthma where the patient has daily attacks for months, a type well suited for a therapeutic study, all attempts at desensitization are usually futile.

Roentgen ray therapy is now quite extensively used in asthma and judging from the reports the results are good. The earlier treatments were given over the chest. This has given place to treatments over the spleen with reported greater relief. The roentgen rays cause cellular injury with the death of some cells, the absorption of this cellular debris is thought to act as a foreign protein, in other words, it may be a form of non-specific desensitization. Groedel, Lossen and Pohlmann (107), Gerber (108), Bergerhoff (109), and others who have treated series of cases claim results unequalled by any other form of therapy.

*Hay fever* The literature contains a few references to non-specific therapy in hay fever. Vaccine made from the predominating micro-organism in the nasal secretion has been used with reported benefit. Van Leeuwen has used tuberculin and Coke (110) colon bacillus vaccine.

#### CHEMOTHERAPY

It has been assumed that specific drugs owe their specificity to their direct action on the parasite. Dale (111) under the title "Progress and Prospects of Chemotherapy," raises the question of the actual

failed to relieve him. He acquired diphtheria and following injection of antitoxin was entirely relieved of his asthma weeks when it returned.

Kahn and Einsheimer (101) reported good results with autohemotherapy. They injected 20 to 30 cc of blood subcutaneously. The blood after coagulation becomes a protein. The literature contains several references to results in asthma with this treatment. The patient receives ten injections at four-day intervals. In case of improvement he may continue to receive injections at two-week intervals until the asthma returns, when two more injections may be sufficient to control the discomfort.

There has been considerable discussion on the value of stock vaccines. It is the writer's experience that asthma is not benefited by stock vaccines will not respond to vaccine.

Rackeman (102) believes vaccine in the treatment of asthma due to its powers to produce a local reaction. He has failed to get results except with a vaccine to produce a local reaction. He believes the vaccine agent exciting it as the essential factor in the desensitization might in itself give rise to a false reaction.

Van Leeuwen (103) is a strong advocate of the treatment of asthma with vaccine. In case of the initial dose is 1 cc given twice a week, increased to 5 cc after a week's reaction. In his selected cases of asthma he has cured completely or almost completely or consistently with "cures" and the reaction is

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tissues it is converted into the highly spirocheticidal oxide of arsenic. If, however, the arsenoxide is administered it is less spirocheticidal than the neoarsphenamin. The explanation offered to overcome this objection is that the arsenoxide, when slowly formed in the tissues, is more efficient than when given directly into the vein.

We are indebted to Levaditi (112) and his colleagues for much interesting information on this subject. In 1905 he worked with atoxyl, finding it only slightly germicidal for the *Spirillum gallinarum*, a spirillum of fowls, *in vitro*. If the atoxyl was mixed with finely chopped rabbit's liver and incubated for two or three hours the mixture became highly germicidal. When the arsenic was separated from the liver it was found that this activity resided in the liver extract. Levaditi (113) later applied this same method of examination with bismuth, again using the *Spirillum gallinarum*. Neither metallic bismuth nor any of its salts had any effect on this parasite *in vitro*. When the bismuth was incubated with fresh organ or tissue extracts it became highly active. When the bismuth was removed from the mixture this activity was found to reside in the tissue extract. Apparently the bismuth acting on the tissue cells or extract led to the formation of a germicidal substance. He states that very small amounts of bismuth were required fully to activate the tissue extract.

He reports that all organ and tissue extracts possess this activating power. Whole blood, washed corpuscles, leucocytes, nucleinic acid and white or yolk of egg, and yeast will not activate the bismuth. Liver extracts from different species varied in activity. The liver of a guinea pig was less active than the liver of fowls or rats. Liver plunged into boiling water for five minutes retained its activity, but it was destroyed by prolonged boiling. This active substance passes through a porcelain filter but not through a collodion sac. It resists desiccation, retaining its activity three months at room temperature. Levaditi's work has not been substantiated, although it is too early to say that it has been disproven. His work, however, forms a basis for an interesting hypothesis, which would enable us to explain certain phenomena.

Tryparsamid has a very low spirocheticidal index. So much so that Brown and Pearce (114) who worked with it in animal syphilis were inclined to discard it as a spirocheticide. In man tryparsamid is



practically valueless except in central nervous system syphilis and especially in paresis. In this latter disease the results are practically the same as those obtained with malaria and like malaria there is no special relationship between the improvement or lack of improvement and the spinal fluid changes. When we say it has a selective action for cerebral syphilis we have merely made a statement and not an explanation. If we accept Levaditi's views that organs vary in their activating power, if we wished to theorize we might say that brain tissue alone can activate tryparsamid.

Atoxyl and tryparsamid are both used in trypanosome infections. An infected mouse if given a dose of atoxyl insufficient to kill the parasite will develop a resistant strain. When these trypanosomes are injected into another mouse they remain resistant to atoxyl. If this strain is introduced into a rat it promptly loses its resistance to the arsenic. It is difficult to explain this phenomenon if we assume that atoxyl acts as a direct trypanocide. If we accept Levaditi's experiments we might say the atoxyl in conjunction with the rat's tissues was able to form a trypanocidal substance of a character capable of affecting this resistant strain. Rosenthal and Petzal (115) report that a mouse inoculated with a fatal dose of trypanosomes if injected at the same time with human serum survives. The serum of an individual with evidence of marked liver involvement does not exert this protective influence. They infer from this that the liver plays an important rôle in activating the serum.

Bayer's "205" in the test tube has little effect on trypanosomes, although 0.05 gram per kilogram of body weight when injected into man or mouse will sterilize the blood in sixteen hours. In the horse or ox infected with the same species of trypanosome it has no effect. Apparently something in the host plays an important rôle in destroying the parasite.

The question of the method of action of so-called specific drugs opens up an interesting speculative field. Can chemotherapy ignore the rôle played by the host in destroying the invaders?

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